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BIOLOGIC EFFECTS OF THYMUS EXTRACT (HANSON)

ACCRUING ACCELERATION IN GROWTH AND DEVELOPMENT IN FIVE SUCCESSIVE GENERATIONS OF RATS UNDER CONTINUOUS TREATMENT WITH THYMUS EXTRACT

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In this investigation we believe that we have learned something suggestive concerning the thymus gland, and, what is equally important perhaps, we have evolved a novel procedure for the study of this and possibly other endocrine organs. Following the continuous administration of thymus extract to successive generations of rats, marked acceleration in the rate of growth and development has been observed during the early life of the offspring, particularly of the third and later generations. Thus the rate of development encountered in the fifth generation of young rats born of four generations of forbears treated with a thymus extract is almost beyond belief.

METHODS OF EXPERIMENTAL PROCEDURE

A colony of 12 white rats was obtained from the Wistar Institute of June 16, 1933. These animals were divided into test and control groups. Up to the time of writing (April 16, 1934) the test animals have received by intraperitoneal injection 1 cc. of thymus extract (Hanson) daily, even during the periods of pregnancy and lactation. Litter mates born to these rats were mated in pairs, when available, and these rats have likewise received intraperitoneal injections of thymus extract, before puberty or after they reached maturity. For convenience, the animals treated before puberty will be designated as the "prepubertal" group, and those treated after maturity, as the "mature" group. "Mature control" designates the

From the Philadelphia Institute for Medical Research (Samuel Bell Jr. Laboratory) in the Philadelphia General Hospital, the Laboratories of the Philadelphia General Hospital and the Hanson Research Laboratory, Faribault, Minn.

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pair corresponding to a mature test pair; "prepubertal control," the pair corresponding to a pair treated before puberty. The rats of each succeeding generation have been so treated, and the effects on the parents and on the offspring have been noted. Thus the original test animals of the first generation (F_0) have received continuous treatment since June 16, 1933; the F_1 generation, since Sept. 10, 1933; the F_2 generation, since Sept. 25, 1933;[1] the F_3 generation, since Jan. 19, 1934, and the F_4 generation, since April 15, 1934. Treatment of the young has usually been begun from the sixteenth to the twentieth day after birth in the prepubertal group and from the fortieth to the sixtieth day in the mature group. Numerous controls have been employed. At the time of writing (April 16, 1934), the fifth generation[2] of thymus-treated rats had been reached and we had between 300 and 400 rats in our colony.

The rats are confined in pairs in circular mesh wire cages, the floor of which is covered with excelsior. Cups for food and water are attached to the wall of each cage. All the rats used have been given a diet containing the following ingredients (parts per 100 parts): rolled oats, 15; hominy, 60; dried meat scraps, 14; dryco, 10, and sodium chloride, 1. To each 100 Gm. is added 1.25 cc.[3] of cod liver oil. Additional nutriment consists of diluted milk daily and greens twice a week. After a time orange juice was added to the diet at the suggestion of Dr. H. H. Donaldson. The quantity of food is not fixed. The rats are given daily rations more than ample for their needs, and the food remaining at the end of twenty-four hours is discarded. Water is ingested ad libitum.

The 12 rats originally used were of Wistar strain and of known age and parentage. Eight of these were divided into mature and prepubertal test and corresponding control pairs, each pair consisting of litter mates. The remaining four mature animals were segregated according to sex. One male and one female were given injections, and the others were used as controls until they were mated after ten months.

Up to April 16, 1934, over a period of ten months, we have followed two pairs of thymus-treated rats in the F_0 generation for ten and six months, respectively. From their offspring, test and control pairs have been mated, and the same procedure has been followed in each succeeding generation. Our experiments can be divided into three groups: (1) those pertaining to continuous treatment, with daily intraperitoneal injections in succeeding generations; (2) those in which treatment (daily injections) was interrupted for one or more generations, and (3) feeding experiments in which the thymus extract was administered by mouth. In group 1 three series of animals were studied: 1A, the original rats given injections of thymus extract (Hanson) since June 16, 1933; 1B, a series of rats subjected to identical treatment (started on Oct. 5, 1933), to act as a control for the first series, and 1C, a series of rats subjected to similar treatment with a new preparation of thymus extract (Hanson) obtained from another source.

From our original colony of rats, 1A, which have received injections of thymus extract (Hanson) since June 16, 1933, 17 litters were born, and from these 7 control and 10 test pairs were mated in the F_1 generation; 23 litters, 9 control and 14 test pairs, in the F_2 generation, and 13 litters, 4 control and 9 test pairs, in the F_3 generation. From this it is apparent that control pairs have been provided for each generation under treatment.

---

1. The parents were treated only one day prior to delivery; the offspring, on the fifteenth day of life.

2. In the text, F_0 animals are referred to as first generation and F_4 as fifth generation, respectively.

3. Gottesman, J., and Jaffe, H. L.: J. Exper. Med. **42**:413, 1925.

Of the straight control animals, 2 pairs of rats yielded 9 litters in the F_1 generation. From these, 2 mated pairs yielded 12 litters in the F_2 generation. No further matings have been made.

NATURE OF THE THYMUS EXTRACT USED

The extract used in these experiments was prepared by Hanson [4] in 1930. The method and nature, briefly, were as follows:

The thymus glands of from 2 to 6 week old calves were extracted in a 0.5 per cent solution of hydrochloric acid with heat. This method of extraction differs from Hanson's method of extracting the parathyroids simply in the degree of acidity used. The thymus extract thus prepared is extremely stable and is entirely potent and satisfactory for injection into rats even after being kept at room temperature for from two and a half to four years. The extract is golden yellow; its taste and smell resembled those of boullion. It has a p_H of about 5 and is nontoxic in relatively large doses and nonirritating locally on injection.

Chemical analysis of this extract made after three years yielded the following values:

	Mg. per 100 Cc.
Total nitrogen (micro-Kjeldahl method)	5.75
Calcium	4.00
Inorganic phosphorus	12.80
Lipoid phosphorus	19.00
Sodium chloride	365.00
Cholesterol	10.00
Uric acid	14.00
Reduced and oxidized sulphur compounds calculated as glutathione	15.8

The strength of the extract used represented 0.6 Gm. of raw calf thymus per cubic centimeter.

BIOLOGIC DATA ON NORMAL AND ON CONTROL RATS

As our test animals evidence precocity, it is essential to keep in mind the normal biologic data as revealed in control animals. Our control data are of several kinds: 1. The data obtained in the study of rats at the Wistar Institute as summarized by Donaldson [5] in his book on "The Rat." 2. Observations on normal controls, 6 Wistar rats (litter mates of corresponding thymus-treated rats) and their descendants, paired and raised in our laboratory on the same food and under the same conditions as the thymus-treated test rats. These control animals received injections of a saline solution of glycerin over a period of months. 3. Observations on special controls, rats born of thymus-treated animals, which were used as controls for each generation. These controls are described later in a special section devoted to interruption of treatment. 4. Observations on a small group of animals on which treatment with an extract of the lymphatic glands is just being started.

4. Hanson, A. M.: Treatment of Cancer with Thymus Extract, J. A. M. A. **94**:653 (March 1) 1930.

5. Donaldson, H. H.: The Rat, ed. 2, Philadelphia, Wistar Institute of Anatomy and Biology, 1924.

In his book on "The Rat" Donaldson gave the following data as the average norms for the rate of development:

Ears open	2½-3½ days
Incisors erupt	8-10 days
Eyes open	14-17 days
Hair obscures genitalia	16 days
Testes descend	40 days
Vagina open	72 days
Menopause occurs	15-18 months

The average norms for our control rats approximate Donaldson's figures closely, as shown in table 1. The chief difference lies in the earlier gonadal development.

TABLE 1.—*Comparison of Our Control Rats with Those of the Wistar Institute*

		Days						
Strain	Number in Litter	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Comment
Wistar Institute	6.1	2½-3½	8-10	16	14-17	40	72	Fed a varied breeders' diet
Philadelphia Institute for Medical Research*	5.0	2½-3	9-10	12-16	14-17	31-40	55-62	Fed an adequate stock diet

* The figures are based on observation of 104 animals.

Biologic data relative to the rats constituting the normal control series from the second generation are given in table 2. The largest number of litters born was 7 in seven months (F_0). The average interval between gestations was thirty-seven days. The average number of offspring in 21 litters was 4.9. The average weight at birth was 4.6 Gm. per litter. The ears opened, the incisors erupted and the eyes opened at the normal time. Hair appeared between the twelfth and the sixteenth day in all the animals except two, in which it appeared between the eighth or ninth and the fifteenth day. The testes descended between the thirty-fifth and the fortieth day except in two animals, and the vagina opened between the fifty-fifth and the sixty-second day. The mortality among our control animals was very high, many of them being destroyed by the parents, eaten or neglected. The number of control animals in the first generation that survived was 9 of 33, and in the second generation, 30 of 70.

RESULTS OF CONTINUOUS TREATMENT OF SUCCESSIVE GENERATIONS OF RATS BY DAILY INTRAPERITONEAL INJECTION OF 1 CC. OF THYMUS EXTRACT—SERIES 1 A

Data Relating to the Growth and Development of Test Rats of the First Generation (F_0) *and Their Controls.*—In the segregated group, the male test animal became somewhat heavier than the control, the

TABLE 2.—*Rate of Development of Albino Rats in the Control Series (Not Treated)*

Parents (No.)*	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Pregnancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
18 and 19	..	8/30/33	7	4.8	4	3	9-10	12-14	16	36	55	9/23/33	70	91	
P P C	89	11/27/33	3	4.5	0	..	..	.....	..	..	..	.....	..	..	Neglected
	27	12/24/33	7	4.3	2	2.5	10	14-16	-16	36	60	.....	..	..	Both males
	46	2/10/34	5	5.0	0	3	10	12-17	17	..	..	.....	..	..	Died at 24 days
	24	3/ 6/34	2	5.2	0	..	..	.....	..	..	..	.....	..	..	Eaten at 1 day
	24	3/30/34	12	...	..	..	..	.....	..	..	..	.....	..	..	Head of 1 animal found
40 and 41	..	11/29/33	8	4.2	0	..	..	.....	..	..	..	.....	..	..	Unfed
P P C	20	12/18/33	9	4.6	0	..	..	.....	..	..	..	.....	..	..	Unfed
	21	1/ 8/34	7	4.6	0	..	..	.....	..	..	..	.....	..	..	Unfed
	22	1/30/34	8	4.3	7	3	9	8-15	15	38	62	2/26/34	..	..	Have not bred
	49	3/24/34	4	5.0	4	..	..	.....	..	..	..	.....	..	..	
								9-15	15	40	55	8/20/33	55	75	
22 and 23	..	7/ 9/33	3	5.6	3	3	9	.....	..	..	..	.....	..	..	Died on following day
M C	134	11/18/33	2	3.0	0	..	..	.....	..	..	..	.....	..	..	Died; crushed
	25	12/13/33	3	...	..	..	..	.....	..	..	..	.....	..	..	Died; unfed
48 and 49	..	9/12/33	1	4.1	0	..	..	.....	..	..	..	.....	..	..	Died; devoured
M C	47	10/26/33	6	3.9	0	..	..	.....	..	..	..	.....	..	..	Died; unfed
	38	12/ 3/33	5	4.1	0	..	..	.....	..	..	..	.....	..	..	
	34	1/ 6/34	6	5.0	5	3	9-10	12-15	14-15	36	..	.....	..	..	All males
	31	2/ 6/34	7	4.7	6	2½	9-10	14-16	15-16	35	..	.....	..	..	All males
	28	3/ 4/34	4	4.9	3	3	10	12-15	16	33	55	.....	..	..	Unmated
	47	4/10/34	5	6.4	5	3	10	12-14	14	31	Not opened	.....	..	..	To be mated
25 and 27	..	.....	..	...	..	..	..	.....	..	..	..	.....	..	..	

* The letters P P C indicate prepubertal control; M C, mature control.

female becoming heavier after mating. In the mated groups no constant effect on the animals' weight was noted. However, as shown in table 3, the test animals seemed to breed more frequently and to have larger litters, the average weight of the young being higher. Thus the mature test pair (rats 20 and 21) cast 9 litters of 78 animals, and the mature control pair (rats 22 and 23) cast 3 litters of 8 animals from July 10, 1933 to March 13, 1934, a period of eight months, at which time the control mother died.[6] The prepubertal test pair (rats 16 and 17) cast 4 litters of 27 animals, the female dying during labor on Nov. 17, 1933, while the corresponding control pair (rats 18 and 19) cast 2 litters of 10 animals for a corresponding period of two months, from Aug. 30 to Nov. 27, 1933.

These figures for the test and control parents should not be regarded as accurately representative. The mature control pair were apparently not good breeders. Table 2 reveals corresponding data on the other untreated animals. The table shows that 1 pair (rats 18 and 19) cast 6 litters of 24 animals and a second pair (rats 48 and 49) cast 7 litters of 34 animals. The average litter, however, contained in each instance less than 5 young, whereas the litters born to the original test animals comprised on an average 7 and 7.8 animals. Only 1 pair of untreated rats had an average of 7 young per litter.

Data Relating to the Growth and Development of Rats of the Second Generation (F_1).—In all 124 rats were born in 17 litters to 4 pairs of test animals of the first generation (F_0) under treatment. The biologic data for this group of animals are summarized in table 3.

Interval Between Gestations: Because of the death of 2 mothers only 1 pair has continued to breed up to the time of writing, having cast 9 litters in eight months. The dates of birth reveal rapid breeding. Thus for the prepubertal test pair (rats 16 and 17) the longest period between births of litters was twenty-seven days and the shortest twenty days. For the mature test pair (rats 20 and 21) the shortest period was twenty-three days, and in 5 instances it was thirty days or less. In the last pair (rats 38 and 39), the intervals were twenty-four and twenty-two days, respectively. The average period between births for the second generation group as a whole was twenty-seven and nine-tenths days.

Size of Litters: The average number of rats to the litter was 7 for the first pair, 8.6 for the second and 6.3 for the fourth, a total of 124 animals for 17 litters or more than 7.3 rats per litter. The third pair had only 1 litter, the number of which was undetermined. Perhaps the contrast between the size of the litters early and late in the fertile period is of significance. Thus for the first 7 pregnancies (rats 20

6. Tables 2 and 3 show the length of the period covered.

TABLE 3.—*Rate of Development of Treated Albino Rats in the Second Generation (F_1)*

Parents (No.)*	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Pregnancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
16 and 17	..	8/30/33	9	4.3	5	2	7	10-14	14	29	30	9/23/33	98	106	
P P T	22	9/21/33	6	4.5	6	2	5	10-12	14	28	30	10/ 5/33	21	42	
	27	10/18/33	4	...	0	..	..	.....	..	..	..	.....	..	..	Litter devoured
	20	11/17/33	8	5.7	..	..	..	.....	..	..	..	.....	..	..	Female died in labor
20 and 21	..	7/10/33	11	5.0	9	2	9	8-10	14	29	35	8/20/33	40	60	
M T	24	8/ 3/33	8	4.9	7	2-2½	8	7-8	14	28	35	10/ 5/33	69	89	
	30	9/ 2/33	9	6.1	8	2	6	7-10	12	21	32	12/19/33	..	..	
	27	9/29/33	5	4.4	4	2	6	6- 8	13	22	35	12/19/33	140	162	
	23	10/22/33	11	4.3	11	2	6	3- 5	14	22	42	10/22/33	70	92	
	27	11/18/33	15	6.0	7	1	1	4- 6	13	21	32	2/ 2/34	68	89	
	51	1/ 8/34	12	6.1	8	1	2	4- 6	12	15	30	1/31/34	65	86	
	36	2/14/34	3	5.0	0	..	..	.....	..	..	..	.....	..	..	Died of starvation
	27	3/13/34	4	6.0	0	..	..	.....	..	..	..	.....	..	..	in 2 days
	40	4/23/34	4	5.2	3	2	2	6-10	10	12	..	.....	..	..	
38 and 39	..	12/20/34	3	4.3	0	..	..	.....	..	..	..	.....	..	..	Died of starvation
M T	24	1/13/34	8	5.0	7	1-2	1-2	7- 8	14	21	..	.....	..	..	All females
	22	2/ 4/34	8	5.0	0	..	..	.....	..	..	..	.....	..	..	Female died in labor

* The letters P P T indicate treated before puberty; M T, treated after maturity.

and 21) the average number of offspring per litter was 9.5 while for the last 3 pregnancies it was 4 or less.

Weight at Birth: The average birth weight per litter was 4.8 Gm. for the young of the prepubertal group (7 litters of 46 animals) and 5.3 for the offspring of the mature group (10 litters of 78 animals). This gave a combined average birth weight of 5.1 Gm. per litter.

Survival of Offspring: Of the 124 offspring in the second generation, 73 (58 per cent) survived. In the test series 16 or more young rats succumbed owing to the mother's death during parturition. The best rate of survival was encountered in the first 7 litters of the mature test animals, 54 out of 71 (76 per cent) young surviving; but only 3 of the 11 animals in the following three litters survived.

Opening of Ears: According to Donaldson, the ears open normally at between 2½ and 3½ days of age, but there is a cellular plug in the meatus which may persist for some time longer. According to Wada,[7] rats can hear at from 9 to 12 days of age. The earlier date is exceptional. Lane[8] regarded 12 days as the earliest age at which he obtained an auditory response.

At birth the external ear appears merely as a nubble or small mass raised above the surface of the skin. Normally a few days after birth a free margin becomes detached which becomes the lobule or external ear. This development is referred to as the opening of the ear. Thus in our second generation test rats the ear opened in two days in all the litters except the sixth and seventh, in which the ears opened on the first day.

Eruption in Incisors: In rats the incisors are the first teeth to appear, eruption occurring at from 8 to 10 days of age. In our prepubertal animals this phenomenon occurred at the age of 7 days in the first litter and of 5 days in the second. The dates of the eruption of teeth in the 9 litters of one mature pair indicated that eruption of the incisors occurred in the first litter at 9 days, in the third, fourth and fifth litters at 6 days and in the sixth and seventh litters at from 1 to 2 days. Thus the eruption of incisors is increasingly accelerated in succeeding litters born to thymus-treated animals. Prolonged treatment of both parents prior to their mating results in a similar precocity in the eruption of teeth.

Appearance of Fur: In the prepubertal group of the second treated generation hair obscured the genitalia as early as the tenth to the twelfth day in the second litter. In the litters born of the mature animals the body was covered between the eighth and tenth day in the first litter,

7. Wada, T.: Anatomical and Physiological Studies on the Growth of the Inner Ear of the Albino Rat, Mem. no. 10, Philadelphia, Wistar Institute of Anatomy and Biology, 1923.

8. Lane, H. H.: Dissert., Princeton University, 1927.

the fifth and eighth day in the fourth litter, the third and the fifth day in the fifth litter and the fourth and the sixth day in the sixth and seventh litters.

Opening of Eyes: According to Donaldson the eyes open on the fourteenth to the seventeenth day, most often on the fifteenth or sixteenth day. King [9] has also observed that in a given litter the eyes of the females usually open several hours before those of the males. In our test animals of the second generation the eyes opened on the fourteenth day in the rats born of the prepubertal group and in the first two litters of the mature group. The time varied between the twelfth and the fourteenth day in the third, fourth, fifth, sixth and seventh litters.

Descent of Testes: In the offspring of the thymus-treated rats of the second generation, the testes descended earlier than in normal rats. Thus in the prepubertal group the descent of the testes occurred from the twenty-third to the twenty-ninth day. In the mature group there is a progressive acceleration in the descent of the testes. In the first litter it occurred at 29 days, in the second at 28 days, in the third, fourth, fifth and sixth at 21 and 22 days and in the seventh at 15 days.

Opening of Vagina: In all the offspring of thymus-treated rats of the second generation, the vagina opened earlier than normal. In the litters born of the group treated prepubertally the vagina opened on the thirtieth day. In the offspring of the group treated after maturity it opened on the thirty-fifth day in the first, second and fourth litters, on the forty-second day in the fifth litter, on the thirty-second day in the third and sixth litters and on the thirtieth day in the seventh litter.

Growth Curve of Animals of the Second Generation: The growth curve of the later litters show a decided increase in weight over the normal. Figure 1 shows the growth curve of the control animals and of the first, fifth and tenth litters of the second generation of test animals.

Because of the possibility of great significance attaching to the data relating to the tenth litter from the original mature test pair (rats 20 and 21) these data are presented here despite the fact that this litter was born subsequent to the preparation of the body of this report (April 16, 1934). This litter of 4 had a birth weight of 5.2 Gm. The ears opened on the second day; the teeth erupted on the second day; hair obscured the genitalia between the sixth and the tenth days; the eyes opened on the tenth day; the testes descended on the twelfth day, and the vagina opened on the thirtieth day. These figures indicate considerable precocity in the development of the tenth litter born to thymus-treated parents.

Summary of Data Relative to the Second Generation.—The foregoing data show that as a result of treatment of the parents the young

9. King, H. D.: Anat. Rec. **27**:337, 1924.

of the second generation were more numerous and somewhat heavier at birth. The rate of mortality in the young was less and the rate of survival greater. The rate of growth and development was but little affected in the animals of earlier litters but became accelerated in the later litters. This acceleration was accruing in character and became definitely manifested only as succeeding litters were born to thymus-treated parents. Moderate precocity was observed in the later litters of second generation rats born of thymus-treated test animals.

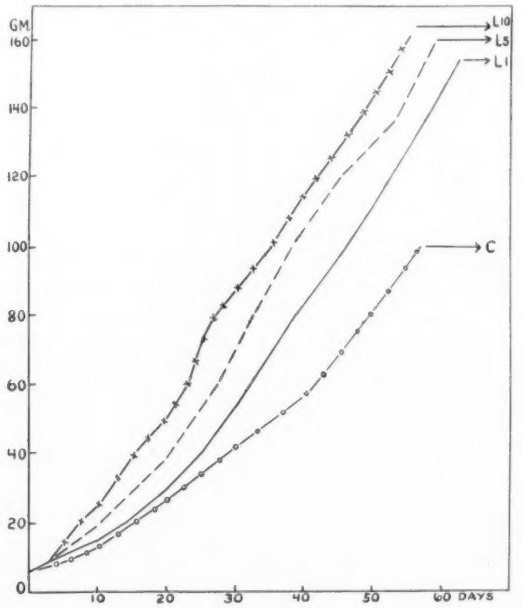

Fig. 1.—Curves showing growth of control litter and of first, fifth and tenth litters of rats 20 and 21.

Data Concerning the Growth and Development of Rats of the Third Generation (F_2).—In all 115 rats were born in 15 litters to 5 pairs[10] of rats of the second generation under treatment with thymus extract. The grandparents and parents, therefore, had received injections of thymus extract. The biologic data concerning rats of the third generation are summarized in table 4.

Interval Between Gestations: Of the 5 pairs of animals bearing in the second generation, the first pair treated (rats 42 and 43) had 2

10. One additional pair (rats 36 and 37), observed for six months, had no offspring.

TABLE 4.—*Rate of Development of Treated Albino Rats in the Third Generation (F_3)*

Parents (No.)*	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Pregnancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
42 and 43	..	9/10/33	6	6.1	6	1-2	1-2	4-6	5	12	31	9/25/33	78	90	
M T	37	10/17/33	7	...	..	..	..	...	..	..	..	.....	..	..	Crushed
58 and 59	..	1/22/34	10	5.1	7	1	1-2	4-6	6	9	28	2/20/34	56	78	
P P T	44	3/ 7/34	8	5.0	5	1-2	2	4	4	5	26	.....	..	..	All females
	40	4/16/34	8	5.8	7	1	1	5	5	5	27	.....	..	..	
62 and 63	..	11/ 2/33	11	5.4	11	1	2	5-6	6	13	30	1/19/34	78	87	
P P T	42	12/14/33	10	5.1	8	2	2	3-5	5	21	32	1/19/34	72	94	Poorly nourished
	45	1/28/34	7	5.0	6	1	1	4-6	6	8	23	2/20/34	48	70	
	25	2/22/34	8	4.5	8	1	1	3-4	4	5	25	3/12/34	55	76	
	45	4/ 8/34	9	6.4	9	1	1	3-5	5	6	25-26	4/21/34	..	..	
68 and 69	..	11/ 2/33	9	6.1	4	2	1-2	3-5	6	12	29	11/ 7/33	61	82	
M T	41	12/13/33	8	5.3	8	1-2	1	3-5	5	12	24	1/19/34	69	90	
	58	2/ 9/34	6	4.9	0	..	..	...	..	..	..	.....	..	..	Neglected and unfed
	30	3/11/34	6	5.4	5	1-2	1-2	3-4	4	5	..	.....	..	..	All males
90 and 91 M T	..	4/ 3/34	3	4.5	0	..	..	...	..	..	..	.....	..	..	Unfed

* The letters M T indicate treated after maturity; P P T, treated before puberty.

litters and since October 1933 has produced no more. The period between these gestations was thirty-seven days. In 1 prepubertal test pair (rats 58 and 59), there were 3 gestations, the intervals being forty-four and forty days, respectively. A second prepubertal test pair (rats 62 and 63) had 5 litters, the interval between gestations ranging from twenty-five to forty-five days, with the latter span the most unusual. A mature test pair (rats 68 and 69) had 4 litters, the interval between gestations ranging from thirty to fifty-eight days, with an average of forty-four days. Another mature test pair (rats 90 and 91) cast 1 litter. The average period between births for the generation as a whole was forty and a half days.

Size of Litters: The largest litter consisted of 11 animals. The average number of rats to the litter was 6.5 for the first pair, 8.7 for the second, 9.4 for the third, 7.5 for the fourth and 3 for the fifth, a total of 115 rats in 15 litters or an average of 7.6 rats per litter.

Weight at Birth: The average birth weight per litter was 5.3 Gm. for the prepubertal group (8 litters of 71 animals) and 5.1 for the mature group (7 litters of 44 animals). This gave a combined average birth weight per litter of 5.2 Gm. for the test pairs.

Survival of Offspring: Of the 115 offspring in the third generation, 84, or approximately 73 per cent, survived.

Opening of Ears: The ears usually opened on the first day; sometimes the process required two days for its completion.

Eruption of Incisors: The incisors usually erupted at about the same time that the ear lobes became detached, that is, from the first to the second day after birth, in most instances at 1 day of age.

Appearance of Fur: The hair obscured the genitalia as early as the third and as late as the sixth day; usually the fur appeared between the fourth and the fifth day.

Opening of Eyes: The eyes opened between the fourth and the sixth day; the earlier date was the usual one for the later litters.

Descent of Testes: In this group the time of the descent of both testes into the scrotum varied markedly from the fifth to the thirteenth day in most instances, but in 1 litter the descent occurred as late as the twenty-first day. Judging by the 2 groups of 5 litters cast, the date of the descent of the testes seems to become progressively more precocious with each succeeding litter. In the offspring of rats 62 and 63 the testes descended in the first litter at 13 days and in the fifth litter at 6 days. In the first litter of rats 68 and 69 the testes descended at 12 days, and in the fourth litter, at 5 days.

Opening of Vagina: In all the offspring of thymus-treated rats of the second generation the vagina opened earlier than normal. This phenomenon occurred between the twenty-third and the thirty-second

day and at a slightly earlier date in each succeeding litter. For instance, in the first litter of rats 68 and 69 the vagina opened on the thirtieth day, and in the fourth litter, between the twenty-fifth and the twenty-sixth day. The earliest opening of the vagina noted in any of the animals of the third generation was on the twenty-third day.

Growth Curve of Animals of the Third Generation: The growth of rats in the third generation was decidedly greater than that of the controls (fig. 2).

Summary of Data Relative to the Third Generation.—In summarizing the results of treatment as observed in animals of the third generation it is found that a striking acceleration of growth and develop-

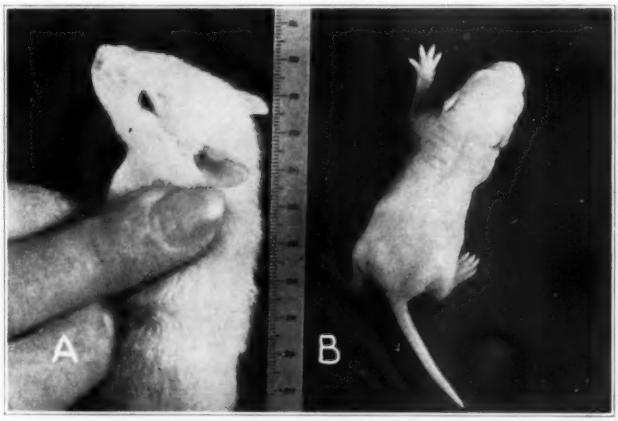

Fig. 2.—Third generation rats: *A*, thymus-treated, 6 days old; *B*, control, 7 days old.

ment occurred. The litters were larger (7.6 animals per litter); the birth weight, 5.2 Gm. per litter, and the rate of survival, 73 per cent, were high. The ears opened and the teeth erupted at the age of from 1 to 2 days; the animals were covered with hair at from 3 to 6 days; the eyes opened at from 4 to 6 days; the testes descended at from 5 to 13 days; the vagina opened at from 23 to 31 days. The animals grew much more rapidly than the control rats of the same group.

Data Relative to the Growth and Development in the Rats of the Fourth Generation (F_3).—The fourth generation consisted of 76 animals born in 12 litters to 5 pairs of rats treated with thymus extract. The great grandparents, grandparents and parents all received injections of thymus extract (Hanson). Biologic data concerning the rats of the fourth generation (F_3) are summarized in table 5.

TABLE 5.—*Rate of Development of Treated Albino Rats in the Fourth Generation (F_3)*

Parents (No.)*	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Pregnancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
50 and 51	..	12/ 8/33	7	5.7	0	..	..	...	..	..	..	.....	..	..	Died, unfed, injured
P P T	29	1/ 6/34	10	5.3	9	1	1	2·6	6	11- 2	24-25	1/31/34	25	44	
	32	2/ 7/34	3	4.9	0	..	..	...	..	..	..	.....	..	..	Unfed
	23	3/ 2/34	5	5.2	5	1	1	2·4	4	6	21	3/12/34	96	..	
	33	4/ 4/34	8	5.0	5	1	1	2·5	5	5	..	.....	..	..	All males
86 and 87 M T	..	3/16/34	4	5.0	4	1	1	4·6	6	6	27	4/ 3/34	..	..	
76 and 77	..	1/28/34	8	5.0	8	1	1	3·4	4	12	25	2/20/34	88	109	
M T	47	3/16/34	3	6.0	2	1	1	2.4	4	6	..	.....	..	..	All males
	25	4/ 8/34	4	6.0	4	1	1	2·4	4	5	..	.....	..	..	All males
80 and 81	..	3/20/34	9	4.8	See comment	1	1	3·4	4	..	..	.....	..	..	Died of starvation 5 days after birth
P P T	14	4/ 3/34	6	6.3	5	1	1	3·5	5	6	24	.....	..	..	
94 and 95 P P T	..	4/10/34	9	4.8	8	1	1	3.5	5	7	22	.....	..	..	

* The letters P P T indicate treated before puberty; M T, treated after maturity.

Interval Between Gestations: The interval between gestations in the third generation was as a rule relatively short and varied from twenty-three to forty-seven days. On two occasions it was twenty-three days. The average interval for the group as a whole was twenty-eight days.

Size of Litters: The litters of the fourth generation were not as large as those of the third. Only once were litters of 10 and 9 animals, respectively, encountered. The average number for the 12 litters was 6.3.

Weight at Birth: As a group the rats of the fourth generation were not larger at birth than those previously observed in the majority of instances. In one litter the average weight was 6.3 Gm. per animal. The average for the group of 78 animals was 5.3 Gm.

Survival of Offspring: Sixty per cent, or a total of 46 animals, survived.

Opening of Ears: The ears opened within twenty-four hours in every rat in the fourth generation.

Eruption of Incisors: The incisors erupted within twenty-four hours in every rat in the fourth generation.

Appearance of Fur: Fur appeared very early in the fourth generation of thymus-treated rats. It was quite marked on from the fourth to the sixth day in all the animals although it appeared from the second to the fourth day in the majority of cases. The rate of development of the hair was unbelievable in many instances; rats showing but a slight down in the morning often had a heavy growth of hair by evening or by the following morning. In the majority of these animals by the fourth or fifth day the fur was far more developed than in the majority of the control animals at the age of 16 days.

Opening of Eyes: The eyes opened on the fourth day in 4 litters, on the fifth day in 3 litters and on the sixth day in 2 litters.

Descent of Testes: The testes descended in some litters as early as the fifth day and in others as late as the twelfth day. In this connection the tables reveal an interesting and significant fact. The descent of the testes occurred much earlier in the litters subsequent to the first in all instances in which several litters of this generation were born to thymus-treated parents. Thus in the litters of the first pair (rats 50 and 51) it occurred on the eleventh and twelfth days in the second litter, on the sixth day in the fourth litter and on the fifth day in the fifth litter. In litters of the third pair (rats 76 and 77) it occurred on the twelfth day in the first, on the sixth day in the second and on the fifth day in the third. This is in keeping with the findings already recorded for testicular descent in the second and third generations of thymus-treated rats.

Opening of the Vagina: The vagina opened in the animals of the fourth generation at from the twenty-first to the twenty-seventh day.

This phenomenon also occurred somewhat earlier in succeeding litters when several litters were born to the same pair. The earliest occurrence was at the age of 21 days, which is somewhat sooner than in the third generation, in which it occurred at 23 days.

Summary of Data Relative to the Fourth Generation.—From these observations it appears that the interval between the casting of litters was short (average twenty-eight days); the number of young in the litters was 6.3; the weight at birth was high, 5.3 Gm., and the rate of survival was 60 per cent. The ears opened and the incisors erupted within twenty-four hours; the animals were covered with hair by the fourth day;

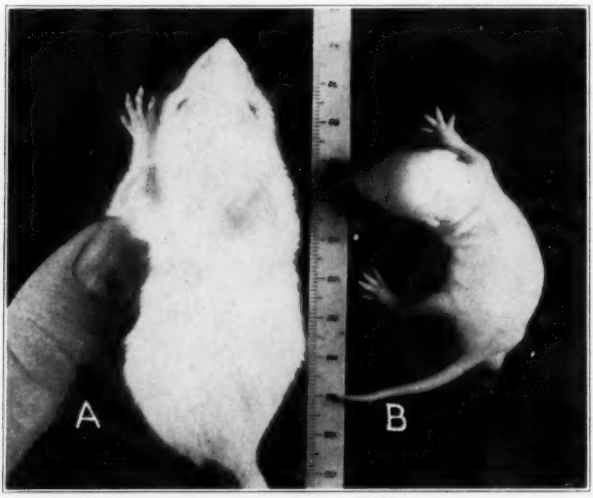

Fig. 3.—Fourth generation rats: *A*, thymus-treated, 6 days old; *B*, control, 7 days old. The eyes of the thymus-treated rat are open.

the eyes opened at from the fourth to the sixth day; the testes descended at from the fifth to the twelfth day, and the vagina opened at from the twenty-first to the twenty-seventh day. The growth of these animals was markedly accelerated.

Data Relative to the Rate of Growth and Development of Rats of the Fifth Generation (F_4).—The fifth generation consisted of 21 rats born to 1 pair (rats 204 and 205), 9 in the first and 12 in the second litter. The interval between the casting of litters was forty-two days. All the rats of the first litter died of starvation at about 3 days of age, probably owing to lack of milk secondary to imperfect development of the mammary glands in a very young mother (43 days old). They lived

long enough, however, to show striking precocity, namely opening of the eyes on the third day (table 6).

Our data on the rate of growth and development in the fifth generation are based on observations in 12 rats of the second litter. The weight at birth was 5.8 Gm. On the first inspection of the animals after birth, the ears were open and the incisors had erupted. The animals became covered with hair between the second and third day, the coat of fur being perfect within 72 hours. In the animals of the surviving group the eyes opened at between 2½ and 3 days of age so that at 72 hours the eyes of all the animals were opened. The testes descended on the fourth day, and the vagina opened on the eighteenth day.

Weaning of Rats of the Fifth Generation on the Third Day: As the 12 animals in this litter had the eyes open on the third day, were

TABLE 6.—*Rate of Development of the Fifth Generation (F_5)*

Parents (No.)	Litter	Date of Birth	Number	Weight at Birth, Gm.	Number Surviving	Opening of Ears†	Eruption of Teeth	Appearance of Hair, Days	Opening of Eyes, Days	Descent of Testes, Days	Opening of Vagina, Days	Comment
204 and 205*	1	2/19/34	9	5.5	See remarks	Birth	Birth	2-3	3	..	..	All young dead on third day, unfed and neglected
	2	4/ 2/34	12	5.8	12	Birth	Birth	2-3	2.5-3	4	18	One pair weaned 4/5/34 and placed in separate cage for mating

* Treated before puberty.
† At first injection, or within twenty-four hours.

covered with fur and were extremely active and intelligent, it was thought worth while to attempt the weaning of 1 pair. Consequently 2 rats were removed from the mother and placed in a cage provided with a Petri dish for food and with small appropriate containers for milk and water. These rats wandered about the cage, walked through the Petri dish and stepped into the containers for milk and water. They began to lick the food, water and milk off their feet and bodies. Within a short time they ate and drank normally. There was no delay in their gain in weight. In fact, they continued to increase steadily in size and weight and gradually outdistanced all their litter mates. For four weeks they each weighed 2 Gm. more than any of their litter mates, and at 25 days of age they weighed 90 Gm., practically 150 per cent more than the control animals of the same age.

Summary of Data Relative to the Ffth Generation.—In summarizing the results of treatment in animals of the fifth generation it is evident

that the weight at birth was very high (5.6 Gm.).[11] The ears were opened and the teeth erupted on the first inspection within twenty-four hours of birth, and the animals were covered with hair by the third day. The eyes opened at between 2½ and 3 days of age; the testes descended by the fourth day, and the vagina was opened by the eighteenth day. Psychic as well as physical precocity was so striking in these rats that two of them were weaned successfully before 3 days of age, and their growth curve surpassed that of their litter mates left with the mother.

Effect of Intraperitoneal Injections of Thymus Extract on Weight.—A study of the weight curves indicates a deficiency in growth in our

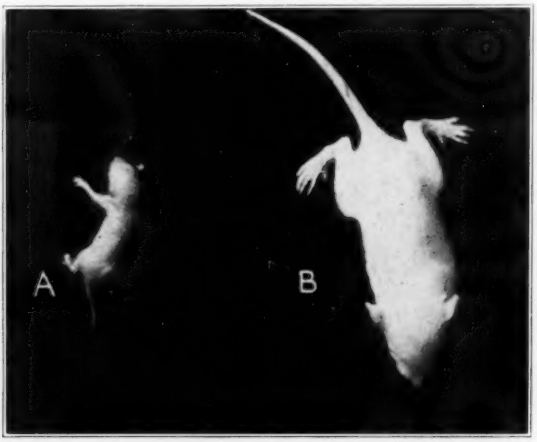

Fig. 4.—Fifth generation rats: *A*, control; *B*, thymus-treated, of same age as control.

control rats after the twentieth day as compared with the figures given by the Wistar Institute and a striking and increasing acceleration in the weight of our thymus-treated animals of the third, fourth and fifth generations and also in the later litters of the second generation. At all times from the fourth to the fortieth day our fifth generation rats weighed more than twice as much as our control rats and up to thirty days of age consistently outweighed the rats of the Wistar Institute. Between the third and the twentieth day our fifth generation rats exceeded the Wistar rats in weight by about 100 per cent. After the sixtieth day these curves tend to come together. These observations will be presented in a later publication.

11. This is the average weight for the group as a whole.

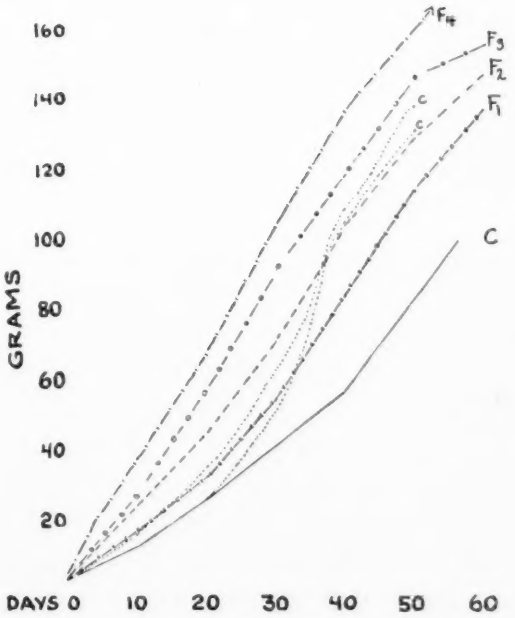

Fig. 5.—Curves showing weight of thymus-treated rats and of control animals.

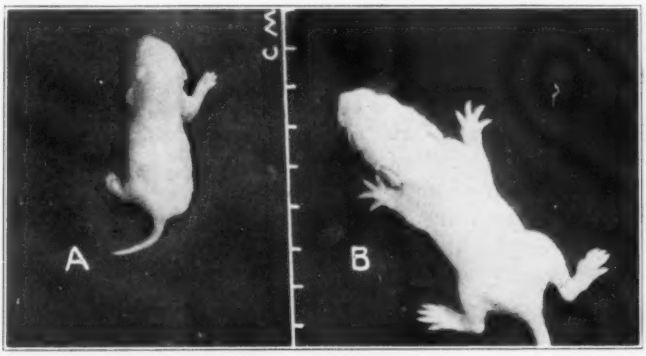

Fig. 6.—Seventh generation rats: *A*, control, 3 days old; *B*, thymus-treated, 45 hours old. The eyes of the thymus-treated rat are open.

RESULTS IN A SECOND SERIES OF RATS UNDER CONTINUOUS TREATMENT WITH DAILY INTRAPERITONEAL INJECTIONS OF THE SAME PREPARATION OF THYMUS EXTRACT (HANSON)—SERIES 1 B

The results of injection of thymus extract in our first series of rats seemed so incredible that we believed confirmatory experiments were necessary. A conference was held with Dr. H. H. Donaldson as soon as the precocity of our third generation test rats was noted. At this conference it was decided to continue the treatment of the original group until 10 litters could be studied and to repeat the experiments starting de novo.

Accordingly, a pair of rats received injections of thymus extract beginning on Dec. 11, 1933. The geneological chart together with the data pertaining to the third generation is shown in table 7. Interest

TABLE 7.—*Second Series of Thymus-Treated Rats* *

Geneology

Rats 74 and 75 (born 8/30/33)—— L_0 F_0
M. T.

F_1

L_1 born 11/11/33 L_2

Rats 212 and 213
M. T.

F_2

L_1 L_2 L_3

Litter	Date of Birth	Weight at Birth, Gm.	Opening of Ears	Appearance of Hair	Opening of Eyes	Number in Litter	Comment
L_1 F_2	2/22/34	5.3	...	...	..	3	All dead on second day
L_2 F_2	3/16/34	4.8	1-2	3-5	6	10	All died of inanition by seventeenth day
L_3 F_2	4/10/34	4.9	1	3-5	5	10	All died of inanition by twelfth day

* In this table "M T" indicates that the rats were treated after they had reached maturity.

centers, of course, on the third generation of thymus-treated rats, the generation which revealed such striking evidence in our original studies.

The period between gestations was short, varying from twenty-two to twenty-five days. Three litters were born between Feb. 22 and April 10, 1934. The average number of rats per litter was 7.6, and the average weight at birth was 5 Gm. The ears opened within two days. The animals were covered with fur in from three to five days, and the eyes opened on from the fifth to the sixth day. While not so extensive as before, these experiments yielded confirmation of our earlier results as to precocity, growth and development in the young of the third generation.

EXPERIMENT WITH A NEW PREPARATION OF THYMUS EXTRACT (HANSON)—SERIES 1 C

All the results so far described have been obtained with the original preparation of thymus extract sent to us by Hanson. As stated, this extract was prepared in 1930 and hence had stood for about two and

TABLE 8.—*Effect of Injection of Thymus Extract (New) on Albino Rats of the Second Generation (F_1)*

Parents (No.)	Litter	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Date of Pregnancy	Date of Casting of First Litter	Comment
74 and 75	2	2/18/34	5	4.9	0	..	..	.....	..	..	..	1/31/34	2/ 1/34	2/22/34	Extravasations about the face and belly
100 and 101	1	12/27/33	7	4.0	0	..	..	.....	..	..	..	.....	.....	.....	Unfed; no milk
	2	2/18/34	7	5.1	3	3	9	11-13	13	27	..	.....	3/12/34	.....	Mated pair died 3/17/34; toxic
	3	3/23/34	5	4.6	0	..	..	.....	..	..	..	.....	.....	.....	Neglected
102 and 103	1	1/25/34	4	5.1	0	..	..	.....	..	..	..	.....	.....	.....	3 crushed at birth; 1 died next day
	2	3/ 2/34	7	4.3	0	..	..	.....	..	..	..	.....	.....	.....	No milk
	3	4/10/34	4	5.0	4	2	8	9-11	11	15	44	5/28/34	.....	.....	

a half to four years before being used. The new preparation of thymus extract was received on Jan. 6, 1934. It was administered intraperitoneally in doses of 1 cc. daily as in the other studies recorded. The treatment has been continued for from four to six months.

The six rats used in this series were born of rats which had received injections of the old thymus extract and represent the second and third (F_1 and F_2) generations under treatment. The results of this experiment were entirely negative as to evidence of precocity in growth and development (table 8). From this it appears that the new preparation of thymus extract was lacking in potency; why, we cannot say. One difference between the old extract prepared by Hanson himself and the new preparation is that Hanson's original extract contained 15.8 mg. per hundred cubic centimeters of reduced and oxidized sulphur compounds calculated as glutathione and this was lacking in the new preparation. This difference may or may not be significant, but the glutathione [11a] content of the extract will be observed in future studies.

EFFECTS OF INTERRUPTION OF TREATMENT OF RATS WITH THYMUS EXTRACT (HANSON)

An effort has been made to determine the effect of omitting the treatment through one or more generations. The results of the studies in the group in which treatment was interrupted are shown in table 9.[12]

Observations on a T C Group.—The first group consisted of the offspring of control patients descended from treated grandparents. In this group there were 7 pairs. The shortest period between pregnancies in this group was twenty-four days; the longest, one hundred and eighty-six days. The largest litter consisted of 11 rats and the smallest of 3. There were 14 litters (90 animals) born of 7 pairs; the average weight at birth was 5.1 Gm. Of the 90 animals, 47 (52 per cent) survived. The ears opened at from the second to the third day. The teeth erupted as early as the third but usually from the eighth to the tenth day. Hair appeared late, from the tenth to the fourteenth day in all the animals except in litters from 1 pair in which it appeared from the third to the fifth day. The eyes opened on from the thirteenth to the fourteenth day in all but the animals born of 1 pair, in which they opened at 5 days in the first litter and at 10 days in the second litter. The testes descended at from the twentieth to the fortieth day in all except the offspring of 1 pair, in which they descended at 12 days in the first litter and at 18 days in the second litter. The vagina opened at ages varying from 20 to 60 days.

11a. Experiments in which glutathione is being used instead of thymus extract are now in progress.

12. In table 9 and in the text T indicates a generation treated with thymus extract, and C represents a control generation, a period with omission of treatment.

TABLE 9.—*Rate of Development of the Albino Rats Under the Influence of Thymus Extract (Hanson) When Treatment is Interrupted Through One or More Generations* *

Parents (No.)	Litter	Period Between Gestations, Days	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating	Pregnancy (Days from Birth)	Casting of First Litter (Days from Birth)	Comment
34 and 35 P P C	1	..	12/14/34	6	...	0	..	..	.....	..	..	..	.....	..	..	Devoured
T-C	2	27	1/10/34	11	4.5	0	..	..	.....	..	..	..	.....	..	..	Unfed
60 and 61 P P C	1	..	1/18/34	5	4.9	0	..	..	.....	..	..	..	.....	..	..	Starved
T-C	2	35	2/22/34	7	5.5	2	3	7-9	9-12	14	20	..	.....	..	..	All males
64 and 65 P P C	1	..	11/15/33	8	4.4	4	2-3	9	10-12	13	40	..	.....	..	..	All males
T-C	2	38	12/23/33	5	4.6	4	2-5	10	10-14	36-40	60	..	.....	..	..	All males
	3	33	1/25/34	6	4.1	0	..	..	.....	..	..	..	.....	..	..	Starved
	4	28	2/22/34	9	4.3	9	3	8	12-14	14	39	45	4/16/34	54	67	
	5	54	4/16/34	7	5.3	7	2	8-10	12-14	14	35	..	.....	..	..	
98 and 99 P P C	1	..	4/ 9/34	5	4.6	0	..	..	.....	..	..	..	.....	..	..	
T-C																
44 and 45 M T	1	..	9/10/33	4	6.3	4	2	3	3-5	5	12	31	9/25/33	67	89	
T-C	2	187	3/16/34	3	5.8	3	2	3	4-6	10	18	..	Killed at 21 days			
92 and 93 M C	1	..	4/ 2/34	6	5.5	6	2-5	8	11-14	14	28	35	.....	..	..	
T-C																
202 and 203 P P C	1	..	4/ 3/34	8	6.2	8	3	7-9	9-12	14	32	..	.....	..	..	All males
T-C																
52 and 53 P P C	1	..	12/ 8/33	5	6.0	0	..	..	.....	..	..	..	.....	..	..	Unfed
T T-C	2	54	1/31/34	1	...	0	..	..	.....	..	..	..	.....	..	..	Born dead
	3	23	2/23/34	2	5.9	0	..	..	.....	..	..	..	.....	..	..	Unfed
	4	23	3/18/34	1	7.0	0	..	..	.....	..	..	..	.....	..	..	Born dead
	5	24	4/11/34	3	4.6	0	..	..	.....	..	..	..	.....	..	..	Neglected
72 and 73 P P C	1	..	1/23/34	6	5.2	0	..	..	.....	..	..	..	.....	..	..	Unfed
T T-C	2	29	2/21/34	5	4.7	4	2-5	8	10-12	12	26	30	4/ 3/34	85	107	
54 and 55 P P T	1	..	12/ 8/33	8	6.0	0	..	..	.....	..	..	..	.....	..	..	Unfed
T C-T	2	33	1/10/34	10	4.6	10	1	1	3-5	5	11	25	1/31/34	74	95	
	3	42	2/11/34	1	6.9	0	..	..	.....	..	..	..	.....	..	..	Unfed
	4	25	3/ 6/34	7	5.4	7	1	1	2-4	5	7	24	.....	..	..	
114 and 115 P P T	1	..	4/29/34	10	5.5	7	2	2	3-5	5	12	..	.....	..	..	
T C-T																
214 and 215 M C	1	..	2/19/34	9	5.0	9	2-5	10	12-16	16	37	..	.....	..	..	
C T-C	2	37	3/28/34	2	...	0	..	..	.....	..	..	..	.....	..	..	Died
	3	19	4/16/34	13	4.8	13	2-5	10	12-14	14	34	..	.....	..	..	
210 and 211 P P C	1	..	4/10/34	3	5.7	3	3	7-8	9-12	14	32	..	.....	..	..	All males
T C T-C																
206 and 207 P P C	1	..	3/16/34	1	7.5	0	..	..	.....	..	..	..	.....	..	..	Unfed
T T T-C	2	23	4/ 8/34	8	5.1	8	2	5	10-12	12	20	..	.....	..	..	

* The data in the table relate to the offspring of the pair signified in the first column to the left. The symbols refer directly to parents, grandparents, great grandparents, etc. The last symbol in each sequence, C or T, refers to parents, the next to the left to grandparents, the next to great grandparents, etc. All the animals referred to in this table represent rats of at least the third generation under observation. For example, T C T-T indicates that the animals are test animals whose parents are test animals, whose gradparents are control animals and whose great grandparents are test animals. P P C indicates control animals for the group treated before puberty; M C, controls for the group treated after maturity.

This analysis indicates that the precocity observed in the third generation of rats born of control parents but of treated grandparents was confined largely to the offspring of 1 pair (rats 44 and 45). The parents were left with the grandparents, the mother nursing from the grandmother until a few days prior to the birth of the first litter. This first litter (L_1) showed considerable precocity as evidenced by the appearance of hair at the age of from 3 to 5 days, the opening of the eyes at 5 days, the descent of the testes at 12 days and the opening of the vagina at 31 days. However, the second litter born six months later to these same parents showed a marked diminution in this precocity, hair appearing at from 4 to 5 days, the eyes opening at 10 days and the testes descending at 18 days.

Observations on T T C Groups.—In two series of animals the parents were not treated, but the grandparents and great grandparents (rats 52 and 53 and rats 72 and 73) had received treatment. The offspring represented the fourth generation under observation. The parents and their litter mates showed marked precocity. Precocity in the offspring of these animals was not pronounced. One pair (rats 72 and 73) had two litters, consisting of 6 and 5 animals, respectively. The average weight at birth was 4.9 Gm. Only 4 animals (second litter) survived. The ears opened at the age of 2½ days; the teeth erupted at 8 days; hair appeared at from 10 to 12 days; the testes descended at 26 days, and the vagina opened at 39 days. Five successive litters born to rats 52 and 53 died within three days of birth owing to neglect on the part of the mother. This may possibly have been due to the lack of milk.

Observations on a T C-T Group.—The next group also comprised the offspring of 1 pair (rats 54 and 55) on which treatment was begun prepubertally. The shortest time between pregnancies was twenty-three days and the longest thirty-three days. The number of litters was 4 and the number of young 26. The average weight at birth was 5.7 Gm. The number surviving was 17, or 65 per cent. In this group the precocity was very striking. The ears opened on the first day, the teeth erupted on the first day, the hair appeared from the second to the fifth day and the eyes opened on the fifth day in every instance. The testes descended at from the seventh to the seventeenth day, and the vagina opened at from the twenty-fourth to the twenty-fifth day. From this it appears that fourth generation rats born of treated parents and great grandparents but of untreated grandparents show striking precocity.

In contrast to this group there were several series of rats in which no treatment had been given except to the grandparents or earlier forebears. The groups are designated as C T C, T C T C and T T T C. Only slight precocity, if any, was encountered in these animals. From analysis of table 9, giving data on 173 animals born in 31 litters to 13

pairs in the series in which treatment was interrupted for one or more generations, it is evident that precocity is lacking or is but slight in all animals born of untreated parents. The effects of treatment through three generations are largely nullified through omission of treatment of the fourth generation. When the effect of treatment is apparent in the offspring of untreated animals it appears, as a rule, only in the first litter, rapidly disappearing in succeeding litters. It seems likely, therefore, that when thymus treatment is discontinued in the parents the effect on the subsequent offspring is quickly apparent.

EXPERIMENTS ON ORAL ADMINISTRATION OF THYMUS EXTRACT

An effort was made to determine whether or not thymus extract is effective when administered by mouth. In order to determine its activity,

TABLE 10.—*Effect of Feeding Thymus Extract (New) on Albino Rats of the Second Generation (F_1)*

Parents (No.)	Litter	Date of Birth	Number in Litter	Weight at Birth, Gm.	Number Surviving	Opening of Ears	Eruption of Teeth	Appearance of Hair	Opening of Eyes	Descent of Testes	Opening of Vagina	Date of Mating
300 and 301	1	3/20/34	6	5.3	6	2	4	9-11	13	26	46	4/16/34
302 and 303	1	3/16/34	6	5.2	6	2	8	10-12	12	29	40	4/20/34
304 and 305	1	2/13/34	9	4.4	6	2	6-8	8-10	9-10	26	35	3/23/34
306 and 307	1	3/10/34	12	6.8	12	2	8	10	12	23	40	4/20/34

the extract was administered orally to 4 pairs of rats, all of which were born of animals having received old thymus extract by injection. In other words, these 4 pairs of animals represented second generation (F_1) rats under thymus treatment. These pairs, had treatment with the old extract been continued by injection, would in all probability have shown the marked precocity already recorded for our third generation (F_2) of thymus-treated rats. Four cubic centimeters of the new thymus extract per rat was administered daily mixed with the food over a period of four months. The food was not entirely consumed each day. Unfortunately only the new thymus extract was used in these experiments and since, as indicated, this was not potent when administered by injection, the results of this study must be considered inconclusive (table 10).

COMMENT

In this communication we have presented detailed evidence of the effect of thymus extract (Hanson) on the growth and development of rats born to succeeding generations of parents under treatment. It is obvious that there is an accruing acceleration of these effects in each

generation. This is strikingly demonstrated in tables 11 and 12. The effect on weight has already been shown in the growth curves.

From our own investigations no claims can be made for the specificity of the thymus extract in connection with the acceleration in growth and development observed. Neither is it apparent whether the extract represents a secretory product, a physiologic hormone of the thymus or a pharmacodynamic agent derived from the thymus.

TABLE 11.—*Comparison of Data on Thymus-Treated Rats with Data on Control Animals*

	Control Animals	F_1*	F_2	F_3	F_4
Number of pairs treated	4	4	5	5	1
Number of litters	21	17	15	12	2
Number of young	103	124	115	76	21
Average number per litter	4.9	7.3	7.6	6.3	10.5
Percentage of survival	37.8	58	73	60	57
Average period between gestations	37	27.9	40.5	28	42
Number of days in which these data were obtained†	(210-300) 239	(80-300) 170	(50-230) 164	(35-201) 120	55

* F_1, F_2, etc., refer to the offspring of treated pairs F_0, F_1, etc.
† The figures in parentheses indicate the range of values; the figures in the lower line indicate the average.

TABLE 12.—*Development of Thymus-Treated Rats as Contrasted with Development of Control Animals*

	Control Animals	F_1	F_2	F_3	F_4
Average weight at birth, Gm.*	4.6	5.1	5.3	5.3	5.6
Opening of ears, days	2½-3½	2	1-2	1	1
Eruption of teeth, days	8-10	1-9	1-2	1	1
Appearance of hair, days	12-16	3-12	4-6	4-5	2-3
Opening of eyes, days	14-17	12-14	4-6	4-6	2-3
Descent of testes, days	35-40	15-29†	5-21†	5-12†	4-5
Opening of vagina, days	55-62	30-45†	23-32†	21-27†	18-19

* These figures are based on 103 animals in the control series and 124 in the F_1, 115 in the F_2, 76 in the F_3 and 21 in the F_4 generation.
† The low numbers usually relate to late litters in the generation and the high numbers to the first litters born.

In addition to these biologic effects there are other manifestations which have not been so well emphasized. These include behaviorism, psychic attributes, the effects on the circulatory system, the fertility of treated females, the influence on test offspring of nursing by control mothers and the effect of thymus extract on new-born rats.

The psychic precocity is as striking as the physical in the thymus-treated strain of rats. Thus fifth generation test animals moved about the cage at 3 days of age and appeared as capable and alert as normal rats of from 16 to 20 days of age. Such animals are able to climb out of a wire net enclosure from 3 to 4 inches high.

Weaning is possible at 3 days of age, the rats finding their water, milk and food supply. They burrow under the excelsior, find a resting place and have no need of further care from the parents.

The thymus-treated animals appear to be in good health, and their reactions asleep or awake resemble in all respects those of normal rats. They are entirely docile and easily handled without gloves. They do not resent puncture with the needle to any great extent and apparently suffer no pain or distress following the injection of thymus extract. We have wondered at times whether the chlorbutanol used as a preservative in this extract in any way accounts for the docility observed.

White rats swim instinctively. Young rats can swim as soon as their eyes open and they are covered with fur. Our third generation rats swam at the age of 6 and 7 days; our fourth generation rats at 4 and 5 days, and our fifth generation rats at from 3 to 4 days. None of these animals entered the water voluntarily, but when thrown into water they appeared at a loss only momentarily and then swam toward the nearest shore. They swam rapidly with their heads well up out of the water. If the water was not too deep, they stood on their hindlegs and made frantic efforts to spring to safety. The control rats could not swim until after the eyes opened, i. e., until from 14 to 16 days of age.

With the amounts of medication employed in these experiments little or no effect can be noted on the circulation of the rat. However, when given in large or toxic doses to either dogs or rats thymus extract exercises a profound effect on the cardiovascular system. Thus in dogs attached to the kymograph the blood pressure fell 14 mm. following an injection of 1 cc., and following an injection of 40 cc. it fell 66 mm. and persisted at this level for sixteen minutes. Electrocardiographic tracings were made for rats in several instances in conjunction with Dr. T. A. McMillan and Dr. Samuel Bellet of the Philadelphia General Hospital. Needles inserted into the muscles of the extremities constituted the electrical contacts. It was found that thymus extract (Hanson) in doses of 1 cc. exercised little or no effect. However, following intraperitoneal administration of 5 cc., cardiac arrythmia developed, ending eventually in auriculoventricular dissociation and complete heart block.

The period between the casting of litters has varied slightly in both control and test animals. However, the averages for each group are of considerable interest. The average time between litters for the control animals has been thirty-seven days, whereas for treated parents it was twenty-seven and nine-tenths days in the F_1, forty and five-tenths days in the F_2, twenty-eight days in the F_3, and forty-two days in the F_4 generation.

New-born rats of the thymus-treated group removed from their mothers [13] and placed with control "wet nurse" rats evidenced precocity comparable to that of litter mates left with thymus-treated parents. This experiment was carried out in several instances in which the litter was too large or poorly fed because of lack of milk or neglect on the part of the mother. Control new-born rats suckled by mothers treated with thymus extract whose litters had evidenced marked precocity manifested no precocity and no increase in the rate of growth and development.

Thymus extract was injected into the new-born control young in several instances; as a rule, no effect was noted during the early stage of growth and development. However, in one group which had received injections the eyes opened prematurely on the tenth day. Injection of thymus extract had no effect whatever on the weight curve, the weight of animals receiving injections corresponding throughout to that of their litter mate controls.

The mortality in the F_1 treated generation was 42 per cent, calculated on 2 litters; in the F_2, 27 per cent; in the F_3, 40 per cent, and in the F_4, 43 per cent. In many instances the rats died owing to lack of milk. The average mortality for the entire thymus-treated group was 38 per cent, while that for the control group was 62.2 per cent from July 9, 1933, to April 16, 1934. This vast difference may possibly be accounted for by the increased number of thymus-treated parents breeding as compared to the control animals.

SUMMARY

The thymus extract prepared from the thymus glands of young calves by Hanson and forwarded to us by him is active. All thymus extracts made by Hanson's method, however, are not equally potent, as evidenced by one preparation submitted from another source.

When injected intraperitoneally, Hanson's extract seems to increase the weight and growth of prepubertal male and of mated mature female rats, but it exerts no noticeable effect on the new-born animals.

Treatment of parent rats seems to increase slightly the number and size of the litters and the weight of the young at birth. The most striking biologic effects are observed in the offspring of successive generations of rats continuously treated by intraperitoneal injection and consist of accruing acceleration in growth and development, namely, early eruption of teeth, appearance of fur, opening of the eyes, descent of the testes and opening of the vagina. While precocity was lacking

13. Studies are being made to determine whether the treatment of the mothers alone or of the fathers alone will result in precocity or whether treatment of both parents is necessary.

in the early litters born of thymus-treated parents in the first generation, it appeared in later litters. This precocity is apparently not effected through the mother's milk. Young rats from thymus-treated strains occasionally matured and bred early when they received injections of thymus extract or not, as both thymus-treated and control rats in the F_1 generation cast litters at forty-two and forty-five days, respectively (rats 62 and 63 and rats 64 and 65). Judging from our experiments, then, it appears that thymus extract (Hanson) affects the fertility and rate of growth and development of white rats.

Interruption of thymus administration for one generation nullified to a large extent the effects of the previous administration of thymus even though the treatment may have extended through several generations of rats.

Rats receiving thymus extract appear unusually docile, healthy and contented.

Excessive amounts of thymus extract result in toxicity, as evidenced by increasing auriculoventricular dissociation and eventual heart block.

CONCLUSIONS

1. Thymus extract (Hanson) has accelerated the rate of growth and development, hastened the onset of adolescence in the offspring of treated rats and increased the fertility of parent rats.

2. This acceleration may be noted in later litters of the second generation but is more marked in each succeeding generation under treatment.

3. The treatment of succeeding generations of parent rats with injections of thymus extract has resulted in the amplification of the effects of thymus extract and has possibly thrown some light on the rôle of the thymus gland.[14]

14. Since this paper was submitted for publication, our attention has been drawn to the section, "Entwicklung und Wachstum" by F. Gudernatsch in Hirsch, Max: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1930. Between 1912 and 1919 Gudernatsch administered dried endocrine glands to successive generations of white rats. Treatment was begun as soon as the nursing period was passed. Gudernatsch observed that the feeding of dried thymus gland brought about the following results: healthy animals, numerous pregnancies, large litters, long life and other biologic changes.

COST OF WORK IN PATIENTS WITH HYPERMETABOLISM DUE TO LEUKEMIA AND TO EXOPHTHALMIC GOITER

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A similarity between exophthalmic goiter and leukemia, especially as regards the ratio of the basal metabolic rate to the basal pulse rate, has been pointed out by Minot and Means.[1] Friedgood [2] reported that a response to compound solution of iodine similar to that seen in patients with exophthalmic goiter was obtained in six of ten patients with lymphatic leukemia. Both of these communications contain further comment on the similarities of the two conditions. Recently Dameshek, Berlin and Blumgart [3] have reported a case of chronic lymphatic leukemia (aleukemic) in which total ablation of the thyroid gland resulted in considerable clinical and hematologic improvement.

We have been more interested in the fundamental differences between exophthalmic goiter and leukemia than in their similarities. We have reported investigations [4] which show that protein catabolism is an important factor in the production of hypermetabolism in the common blood dyscrasias. One difference between exophthalmic goiter

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† Dr. Baldridge died Nov. 22, 1934.

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1. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Ratio in Exophthalmic Goiter and in Leukemia, Arch. Int. Med. **33**:576 (May) 1924.

2. Friedgood, H. B.: The Effect of Lugol's Solution on Chronic Lymphatic Leukemia and Its Bearing on the Pathogenesis of Exophthalmic Goiter, Am. J. M. Sc. **183**:515 (April) 1932.

3. Dameshek, W.; Berlin, D. O., and Blumgart, H. L.: Complete Ablation of the Thyroid Gland in a Case of Chronic Lymphatic Leukemia with Hypermetabolism, New England J. Med. **210**:723 (April 5) 1934.

4. Baldridge, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: I. In Pernicious Anemia, J. Clin. Investigation **10**:529 (Aug.) 1931; Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia, Arch. Int. Med. **51**:589 (April) 1933. Barer, A.; Paul, W. D., and Baldridge, C. W.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: III. In Polycythemia Vera, J. Clin. Investigation **13**:15 (Jan.) 1934.

and leukemia has impressed us. It is well known that after some experience one is able to estimate the basal metabolic rate of a patient with exophthalmic goiter with considerable accuracy by considering the clinical evidences of consumption of fuel, production of heat and circulatory changes incident to increased minute volume flow of blood. By using the same criteria our attempts to estimate the metabolic rate of patients with leukemia prove to be most erratic. Neither the loss of weight nor the increase in appetite appears to be as regular or as marked in patients with leukemia as in patients with exophthalmic goiter even though the degree of hypermetabolism is comparable.

Plummer and Boothby,[5] as well as Smith,[6] have demonstrated that patients with exophthalmic goiter work much less efficiently than normal persons. We now wish to report studies in which we compared the efficiency of patients with exophthalmic goiter with that of patients with a similar degree of hypermetabolism due to leukemia.

METHOD

The patient was up and about the ward for at least three days before the tests were made. During this time the patient was put on the treadmill in order that he might become accustomed to it and in order to determine the speed at which he could walk without exhaustion (usually 60 to 70 meters per minute). On the morning of the test the patient, in the postabsorptive state, was taken to the laboratory on a cart. He stood quietly on the treadmill for five minutes during which time the expired air was collected in the first of four Douglas bags by means of an orinasal mask. The air expired during the five minute walking period was collected in bag 2. The expired air was also collected in separate bags during a third and a fourth five minute period. The volume of gas in each bag was measured by a wet gas meter, and the analysis was made with the Haldane apparatus. The metabolism while standing was determined from the first five minute period. The total increase in consumption of oxygen during the periods of walking and of recovery was considered to represent the oxygen required for walking. The number of steps was recorded on a kymograph, and a "work adder" measured the total amount of elevation of the body during walking. The treadmill was similar to that described by Benedict and Murschausen.[7]

The metabolism while standing was used as a basis for determining the cost of walking. For purposes of comparison, values are given in gram calories used in moving 1 Kg. 1 meter horizontally. Although the actual amount of energy necessary to raise and lower the body has been calculated, no attempt has been made to separate this factor from the total energy used in walking as far as tables 1 and 2 are concerned. The theoretical normal has been calculated according to

5. Plummer, H. S., and Boothby, W. M.: The Cost of Work in Exophthalmic Goiter, Am. J. Physiol. **63**:406, 1923.

6. Smith, J. H.: Basal Metabolism: III. Influence of Work with Special Reference to the Thyroid Gland, Arch. Int. Med. **42**:47 (July) 1928.

7. Benedict, F. G., and Murschausen, H.: Energy Transformations During Horizontal Walking, Publ. no. 231, Carnegie Institution of Washington, 1915, p. 34.

the method of McClintock and Paisley.[8] The cost of transporting 1 Kg. 1 meter horizontally has been considered to be 0.538 calories [9] for men from 25 to 29 years of age and 0.52 for women of the same age. The latter figure is an average of the results given by Smith and Doolittle [10] in their table 4.

RESULTS

In two patients with leukemia the basal metabolic rate was definitely within normal limits. The patient E. A. was tested on two occasions about six months apart, and during the second test period her average basal metabolic rate was only 5 per cent above normal. Comparisons will be based on the average results in eleven patients with leukemia and eight patients with hyperthyroidism, in all of whom there was hypermetabolism. The average basal metabolic rate in the patients with leukemia was 38 per cent above normal while that of the patients with hyperthyroidism was increased 40 per cent. Eight of the eleven patients with leukemia were men, while all of the patients with hyperthyroidism were women. The patients with leukemia averaged almost 15 years older than those of the other group.

In all patients the respiratory metabolism was determined in the postabsorptive state. In the patients with leukemia the metabolism while standing was about 18 per cent higher than the true basal metabolism, while in the patients with hyperthyroidism the difference amounted to 23 per cent. Only three of the patients, all of whom had leukemia, had been confined to bed for any appreciable time before the tests were made. These three patients (G. A., J. R. and G. N.) walked about the ward three days before the tests were made, but even so the increase in metabolism incident to standing averaged about 32 per cent of the basal rate, whereas in the other eight subjects the increase was only 11 per cent. The latter figure is comparable to the 12 per cent increase in normal subjects reported by Smith.[11]

Tables 1 and 2 indicate that the cost of work in the patients with hyperthyroidism averaged about 38 per cent above the calculated normal, while in patients with leukemia the corresponding figure was 8.5 per cent below normal. Marked as this difference is it does not represent the whole picture. The cost of work was determined with the metabolism while standing as a base-line, and the metabolism while standing was 5 per cent lower in the patients with leukemia than in those with

8. McClintock, J. T., and Paisley, S.: Cost of Work in Relation to Basal Metabolism, Proc. Soc. Exper. Biol. & Med. **30**:162 (Nov.) 1932.

9. Smith, H. M.: Gaseous Exchange and Physiological Requirements for Level and Grade Walking, Publ. no. 309, Carnegie Institution of Washington, 1922, p. 143.

10. Smith, H. M., and Doolittle, D. B.: Energy Expenditure of Women During Walking at Different Speeds, J. Biol. Chem. **65**:665 (Oct.) 1925.

11. Smith,[9] p. 101.

hyperthyroidism. On the average the patients with leukemia did 26 per cent more kilogram-meters of work in raising and lowering their bodies than was done by the patients with hyperthyroidism. The relationship between the basal metabolism and the cost of walking has been estab-

TABLE 1.—*The Cost of Work in Patients with Leukemia*

Subject	Age, Years	Sex	Average Basal Metabolic Rate, Percentage	Gram Calories per Kg. = M.		Deviation, Percentage	Respiratory Quotient		Kind of Leukemia
				Calculated Normal	Determined		Standing	Walking and Recovery	
E. A.	43	F	+ 5	0.502	0.552	+ 9	0.775	0.784	Myelogenous
W. H.	58	M	+11	0.489	0.534	+ 9	0.802	0.754	Lymphatic
G. A.	46	M	+13	0.505	0.359	−21	0.756	0.833	Myelogenous
T. N.	73	M	+26	0.465	0.427	− 8	0.788	0.831	Myelogenous
H. W.	62	M	+27	0.481	0.396	−19	0.803	0.867	Lymphatic
E. G.	41	F	+29	0.502	0.560	+12	0.708	0.742	Myelogenous
E. A.	43	F	+35	0.502	0.516	+ 3	0.785	0.780	Myelogenous
S. S.	53	M	+42	0.494	0.413	−16	0.736	0.731	Lymphatic
N. E.	51	F	+44	0.490	0.517	+ 5	0.691	0.769	Myelogenous
L. C.	41	M	+45	0.511	0.343	−33	0.690	0.725	Myelogenous
J. R.	60	M	+49	0.481	0.525	+ 9	0.728	0.780	Lymphatic
R. E.	38	M	+52	0.511	0.409	−20	0.686	0.734	Myelogneous
G. N.	61	M	+57	0.481	0.454	− 6	0.660	0.699	Lymphoma, lymphobastic type
Average	52	..	+38	0.493	0.447	− 8.5	0.730	0.774	

TABLE 2.—*The Cost of Work in Patients with Hyperthyroidism, Myxedema and Mitral Stenosis*

Subject	Age, Years	Sex	Average Basal Metabolic Rate, Percentage	Gram Calories per Kg. = M.		Deviation, Percentage	Respiratory Quotient	
				Calculated Normal	Determined		Standing	Walking and Recovery
Hyperthyroidism								
G. F.	44	F	+13	0.497	0.620	+25	0.824	0.831
V. R.	20	F	+21	0.524	0.595	+13	0.805	0.777
T. H.	43	F	+32	0.502	0.759	+51	0.784	0.800
C. J.	38	F	+39	0.509	0.779	+53	0.748	0.774
H. M.	24	F	+42	0.524	0.610	+16	0.709	0.797
V. A.	27	F	+50	0.520	0.789	+52	0.719	0.785
A. V.	53	F	+55	0.490	0.701	+43	0.744	0.807
R. S.	49	F	+67	0.497	0.749	+51	0.736	0.816
Average	37	..	+40	0.508	0.700	+38	0.758	0.798
Myxedema								
L. S.	25	F	−42	0.520	0.423	−19	0.760	0.817
Mitral Stenosis								
J. H.	45	F	− 3	0.497	0.544	+ 9	0.666	0.732
H. W.	27	F	− 3	0.520	0.488	− 6	0.714	0.715

lished by McClintock and Paisley [8] for children, by Smith [9] for young men and by Smith and Doolittle [10] for young women. We have assumed that these figures obtain in older persons, and it follows that because of differences in age and sex the patients with leukemia had a calculated efficiency 3 per cent greater than those in the other group. Each of these three circumstances tends to widen the already marked disparity

in the efficiency with which forward progression with its associated movements can be accomplished in these two groups of patients.

The metabolism of the two groups as calculated in calories per square meter per hour is presented in tables 3 and 4. Here again we found a greater increase in the metabolism while standing and walking in the patients with hyperthyroidism than in those with leukemia. In

TABLE 3.—*Metabolism of Patients with Leukemia Calculated in Calories per Square Meter per Hour*

Subject	Calories per Square Meter per Hour				Speed, Meters per Minute	Deviation from Basal Metabolic Rate	
	Normal	Basal	Standing	Walking		Standing	Walking
E. A.	35.3	37.1	43.2	113.6	60.0	+16	+206
W. H.	36.6	40.5	48.2	123.7	73.4	+19	+205
G. A.	37.8	42.9	57.9	104.8	63.4	+35	+144
T. N.	34.8	43.9	43.1	96.3	64.3	− 2	+119
H. W.	36.0	45.6	58.6	112.9	71.4	+28	+147
E. G.	35.3	45.4	54.9	127.6	66.8	+21	+181
E. A.	35.3	47.6	54.3	114.3	65.9	+14	+140
N. E.	34.5	49.6	53.4	113.4	52.1	+ 7	+129
S. S.	37.2	53.1	60.4	120.8	64.6	+13	+127
L. C.	38.3	55.7	57.1	98.1	58.5	+ 2	+ 76
J. R.	36.0	53.6	69.7	135.8	65.6	+30	+153
R. E.	39.2	59.6	70.0	131.7	64.9	+17	+121
G. N.	36.0	56.7	74.2	127.5	55.1	+30	+124
Average	36.4	50.3	59.4	116.6	63.0	+18	+133

TABLE 4.—*Metabolism in Patients with Hyperthyroidism, Myxedema and Mitral Stenosis Calculated in Calories per Square Meter per Hour*

Subject	Calories per Square Meter per Hour				Speed, Meters per Minute	Deviation from Basal Metabolic Rate	
	Normal	Basal	Standing	Walking		Standing	Walking
Hyperthyroidism							
G. F.	35.3	39.9	48.1	125.5	64.7	+21	+215
V. R.	36.9	44.5	47.1	113.7	70.2	+ 6	+156
T. H.	35.3	46.6	71.9	169.6	59.0	+54	+264
C. J.	35.8	49.9	59.2	149.0	65.4	+19	+199
H. M.	36.9	52.3	64.6	153.1	70.8	+24	+193
V. A.	36.6	55.0	62.6	129.5	52.5	+12	+135
A. B.	34.5	53.4	64.5	144.8	66.0	+21	+171
R. S.	35.0	58.3	73.3	160.7	66.1	+26	+158
Average	35.8	50.0	61.4	143.2	64.3	+23	+186
Myxedema							
L. S.	36.6	21.2	29.1	70.0	57.0	+37	+230
Mitral Stenosis							
J. H.	35.0	34.0	45.0	119.0	69.2	+32	+250
H. W.	36.6	35.2	44.5	104.4	69.4	+26	+197

the tables the calculated normal is included because of the variations dependent on age and sex. The metabolism while walking was determined during five minutes of actual walking and does not take into account the oxygen debt. In the patients with hyperthyroidism the metabolism while walking was about 186 per cent higher than the determined basal metabolism while in the patients with leukemia it was 133 per cent higher.

A number of the patients in both groups complained of shortness of breath on exertion. In only one patient (G. N.) was there definite edema of the ankles. One patient (A. V.) had auricular fibrillation. In an attempt to control the effect of these cardiac difficulties we tested two women with mitral stenosis, both of whom were short of breath on exertion but neither of whom was edematous. It will be seen that the cost of work in these two subjects was within normal limits.

One patient with myxedema was also tested, and the results are included for purposes of comment.

COMMENT

No matter what method is used in comparing the efficiency of walking in patients with hyperthyroidism with that of patients with leukemia it becomes obvious that the two groups are quite different.

Plummer and Boothby concluded that hyperthyroidism "is associated not only with a characteristic increase in the number of useless extraneous movements but further each movement requires approximately twice the normal amount of energy for its accomplishment. Muscular tissue with a resting metabolism increased above normal by thyroxin cannot utilize any portion of this extra heat for the production of motion."

Smith found that patients with hyperthyroidism used more oxygen in holding up a weight than did normal subjects. Plummer and Boothby studied six patients with exophthalmic goiter; Smith studied twelve subjects with toxic goiter, and we have studied eight patients in whom hypermetabolism can be attributed to increase of thyroid secretion. The results are in accord in that patients with hyperthyroidism require an excessive amount of oxygen to accomplish a given amount of work. Our data do not show, as did those of Plummer and Boothby, that "each movement requires approximately twice the normal amount of oxygen for its accomplishment." Even the most casual observation of these two groups of patients on the treadmill leads one to the conclusion that patients with hyperthyroidism are wasteful of oxygen because of increased muscle tone and purposeless movements. It seems possible that an increase in muscle tone and extraneous movements may account for the 38 per cent increase in oxygen used by our subjects with hyperthyroidism in walking. This explanation would obviate the necessity for assuming any basic change in the chemical mechanism of muscle contraction.

Two of the patients with hyperthyroidism (G. F. and T. H.) had been receiving compound solution of iodine before the tests were made. The basal metabolic rate decreased from 67 per cent above normal to 7 per cent above normal in G. F., and the exact amount of decrease in T. H. is not known. In both subjects the cost of work was high.

It would be interesting to know whether compound solution of iodine affects only the metabolism while resting in patients with hyperthyroidism or whether it also brings about an increase in the efficiency with which work can be done. The patient V. R., who walked more efficiently than any other subject with hyperthyroidism, had a nodular goiter for years and showed symptoms of hypermetabolism after taking iodine. Most of the patients with hyperthyroidism showed a slight but definite decrease in the cost of work when the tests were repeated on three successive days. This was not true of the other patients, and it is probably related to the nervous instability of the subjects with hyperthyroidism.

The conclusion that some patients with leukemia can convert some of the excess heat which is produced at rest into motion might seem inescapable at first glance. A possible source of this heat which may be converted to kinetic energy is hard to determine. The patients were all in the postabsorptive state when the tests were made. We have previously demonstrated that the specific dynamic effect of catabolized body protein accounts for some of the hypermetabolism seen in the blood dyscrasias. Several investigators have presented data which show that the heat incident to the specific dynamic action of protein cannot be converted to kinetic energy, whereas the specific dynamic effect of carbohydrate is not apparent if absorption takes place during muscular activity. These experimental results have been well summarized by Lusk.[12]

It therefore appears that that part of the hypermetabolism in leukemia which is due to the specific dynamic action of catabolized endogenous protein cannot be converted to energy for muscular movements. While endogenous protein was not involved in any of the experiments cited by Lusk, there is no experimental evidence that endogenous and exogenous protein are in any way dissimilar in their specific dynamic effects. Since the patients were in the postabsorptive state there is no reason to attribute any part of the production of heat to the specific dynamic effect of carbohydrate or fat. Tempting as it is to attribute part of the economy of muscular effort in some patients with leukemia to a conversion of basal heat to kinetic energy it must be admitted that the present evidence is not sufficient to warrant such an explanation. In the patient with myxedema there certainly was no excess of heat while resting which might have been transformed to kinetic energy.

The respiratory quotients were usually higher during walking than during standing. This was true in both groups, although some of the

12. Lusk, G.: The Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 408.

respiratory quotients for the patients with leukemia were exceedingly low. However, the respiratory quotients for these few patients varied so much that conclusions drawn from a study of them would be of doubtful value.

We have not found the secret of the economy in muscular movement displayed by some patients with leukemia. We have demonstrated a definite difference between the hypermetabolism of exophthalmic goiter and that of leukemia. This difference affords a reasonable explanation for the fact that patients with marked hypermetabolism due to leukemia can work and yet maintain their body weight fairly well without the excessive appetite usually seen in patients with exophthalmic goiter.

The results obtained in the one case of myxedema are of special interest because of the number of patients with cardiac disease who are being subjected to total ablation of the thyroid gland. The patient with myxedema converted calories to kilogram-meters of work very efficiently, as 25 per cent of the total energy produced during walking (including the oxygen debt) would have been necessary to raise and to lower the body if the efficiency in transforming calories to kinetic energy had been 100 per cent. In the patients with leukemia only about 15 per cent of the total energy would have been necessary to raise and to lower the body, and the figure was also 15 per cent for the patients with mitral stenosis. Less than 10 per cent of the total energy produced by the patients with hyperthyroidism would have been necessary to raise and to lower the body if an efficiency of 100 per cent could have been attained. In these calculations it was considered that the energy necessary to lower the body was 52 per cent of that necessary to raise it.[13]

SUMMARY

In eleven patients with leukemia the basal metabolic rate varied from 13 to 57 per cent above normal (average, + 38 per cent). The cost of walking varied from 12 per cent above normal to 33 per cent below normal (average of twenty-three tests, — 8.5 per cent). The average metabolism while standing was 18 per cent above the average basal metabolic rate (normal, about 12 per cent).

In eight patients with exophthalmic goiter the basal metabolic rate varied from 13 to 67 per cent above normal (average, + 40 per cent). The cost of walking varied from 13 to 53 per cent above normal (average of twenty tests, + 38 per cent). The average metabolism while standing was 23 per cent above the average basal metabolic rate. One patient with myxedema (basal metabolic rate, — 42 per cent) used 19 per cent less energy than normal in walking.

13. Amar, Jules: The Human Motor, London, G. Routledge & Sons, 1920, p. 359.

TREATMENT OF CONGESTIVE HEART FAILURE AND ANGINA PECTORIS BY TOTAL ABLATION OF THE NORMAL THYROID GLAND

XVI. THE SENSITIVITY OF MAN TO EPINEPHRINE INJECTED INTRAVENOUSLY BEFORE AND AFTER TOTAL THYROIDECTOMY

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In an earlier communication which presented the therapeutic results following total ablation of the normal thyroid gland in patients with angina pectoris or congestive failure [1] it was stated that "the manner in which relief is afforded by removal of the thyroid gland probably involves several different, though related, mechanisms. The decreased amount of work by the heart, the decreased metabolism of the heart itself, and the decreased sensitivity to epinephrine are some of the possible factors that are being studied." The purpose of this communication is to present studies of the latter factor, namely, the sensitivity of the cardiovascular system to epinephrine before and after total thyroidectomy. Three aspects of the physiologic action of epinephrine in man have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic heart failure; (2) the sensitivity to epinephrine of patients at various levels of basal metabolism and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs in patients with angina pectoris or chronic cardiac disease following total ablation of the thyroid gland.

Previous studies of the physiologic action of epinephrine have been confined for the most part to experimentation on animals. It has been

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From the Medical Service and Research Laboratories of the Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **52**:165 (Aug.) 1933.

shown [2] that there are marked differences in the response of various species to a given dose of this drug. For this reason it is difficult to interpret clinical conditions in man on the basis of results of experiments on animals. Furthermore, since angina pectoris and congestive cardiac disease are clinical entities which have no close counterpart in laboratory animals our studies have been limited to observations on man.

In most investigations of the response to injections of epinephrine the drug has been administered intramuscularly or subcutaneously. Under such conditions, however, absorption is irregular,[3] and hence the action may vary, particularly since small doses may have an effect strikingly different from that of large doses.[4] Weinberg,[5] Cori and Buckwald [2c] and Weiss [6] have shown that with proper precautions intravenous administration of epinephrine to human beings is safe and feasible and that the pharmacologic effect is immediate and closely related to the rate of injection.

In view of the considerations just outlined, our studies of the action of epinephrine have been made in man, with solutions of epinephrine of known concentration injected by continuous intravenous drip under accurately controlled conditions.

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2. (*a*) Cori, C. F.; Cori, G. T., and Buckwald, K. W.: The Mechanism of Epinephrine Action: VI. Changes in Blood Sugar, Lactic Acid and Blood Pressure During Continuous Intravenous Injection of Epinephrine, Am. J. Physiol. **93**:273, 1930. (*b*) Cori, C. F., and Cori, G. T.: Absorption of Epinephrine from the Subcutaneous Tissue of the Rat, Proc. Soc. Exper. Biol. & Med. **27**:558, 1930. (*c*) Cori, C. F., and Buckwald, K. W.: Effect of Continuous Intravenous Injection of Epinephrine on the Carbohydrate Metabolism, Basal Metabolism and Vascular System of Normal Men, Am. J. Physiol. **95**:71, 1930. (*d*) Dragstedt, C. A.; Wightman, A. H., and Huffman, F. W.: The Hemodynamic Action of Minimal Effective Doses of Epinephrine in the Unanesthetized Dog, ibid. **84**:307, 1928. (*e*) Trendelenburg, P., and Fleischhauer, K.: Ueber den Einfluss des Zuckerstiches auf die Adrenalinsekretion der Nebennieren, Ztschr. f. d. ges. exper. Med. **1**:369, 1913.

3. Luckhardt, A. B., and Koppanyi, T.: Conditions Under Which Subcutaneously Injected Epinephrine Gives a Hemodynamic Effect, Proc. Soc. Exper. Biol. & Med. **23**:774, 1926. Lilienthal, H.: Epinephrine: A Method of Prolonging Its Effect in Asthma and the Depression of Shock, J. A. M. A. **90**:1192 (April 14) 1928.

4. Moore, B., and Purinton, C. O.: Ueber den Einfluss minimaler Mengen Nebennierenextracts auf den Arteriellen Blutdruck, Arch. f. d. ges. Physiol. **81**:483, 1900. Hoskins, R. G., and McClure, C. W.: The Adrenal Glands and Blood Pressure, Arch. Int. Med. **10**:343 (Oct.) 1912. Cannon, W. B., and Lyman, H.: The Depressor Effect of Adrenalin on Arterial Pressure, Am. J. Physiol. **31**:376, 1913.

5. Weinberg, F.: Die Dosierung des Adrenalins bei der intravenösen Dauerinfusion, Klin. Wchnschr. **4**:967, 1925.

6. Weiss, S.: Drugs Used in the Treatment of Cardiovascular Diseases: I. Epinephrine and Ephedrine Groups, Mod. Concepts Cardiovascular Dis. **3**:3, 1934.

METHODS AND SUBJECTS

The solution of epinephrine used for intravenous administration was freshly prepared by dilution from the clear, colorless content of ampules of a 1:1,000 solution of epinephrine, sterile physiologic solution of sodium chloride being added to make a dilution of 1:100,000 or 1:200,000. The solution was delivered by gravity from a graduated buret, the tip of which was connected with an 18 gage needle by means of rubber tubing. The rate of flow was accurately controlled by a fine needle valve inserted in the rubber tubing. The solution of epinephrine was administered in the antecubital vein of the left arm. Readings of the buret were made at thirty second intervals throughout the experiment, and the flow was maintained at the desired constant rate.

The measurements of blood pressure were made by the auscultatory method with a mercury manometer, with the standard cuff attached to the right arm. The heart rate was obtained either by means of continuous electrocardiographic tracings, using anteroposterior chest leads, or by use of a stethoscope strapped to the precordium, the number of beats in fifteen seconds being counted. For patients with cardiac irregularities the electrocardiographic method was used exclusively; for other patients the two methods were used interchangeably and gave essentially the same results. The basal metabolic rate and the consumption of oxygen were measured by means of a Benedict-Roth metabolism apparatus. From the curves obtained the respiratory rate, tidal air and respiratory minute volume were estimated. The basal metabolic rate was calculated according to the Aub-DuBois normal standards.[7] Measurements of blood sugar were made by the method of Folin and Wu.[8] The exercise tolerance of patients with angina pectoris was measured by the method of Riseman and Stern.[9]

The response to epinephrine was measured in seventeen subjects, eight men and nine women, whose ages varied from 18 to 64 years. Eighty-six studies of the effect of the intravenous injection of epinephrine were made.

Five patients, three with angina pectoris and two with rheumatic cardiac disease and congestive failure, were tested when the basal metabolic rate was normal and subsequently when various degrees of hypothyroidism developed following total ablation of the thyroid gland.

Two patients with myxedema were tested when the basal metabolic rate was approximately minus 30 per cent and also when the metabolism had been raised to normal by the oral administration of thyroid. One of these patients had spontaneous myxedema which developed several years following subtotal thyroidectomy performed for diffuse nodular goiter; the other patient had diabetes mellitus and myxedema induced by total ablation of the normal thyroid gland. The latter also had mitral stenosis, but at no time had she experienced signs or symptoms of cardiac failure nor had her activities been limited by the cardiac condition.

In addition to the aforementioned seven patients whose sensitivity to epinephrine was measured at different basal metabolic levels, ten other patients were

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7. Aub, J. C., and DuBois, E. F.: Clinical Calorimetry: XIX. The Basal Metabolism of Old Men, Arch. Int. Med. **19**:823 (May) 1917.

8. Folin, O., and Wu, H.: A System of Blood Analysis: Supplement. A Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

9. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Use in Patients with Angina Pectoris on Exertion, Am. J. M. Sc. **188**:646, 1934.

studied at a single metabolic level. The basal metabolic rate in these patients ranged between plus 12 and minus 34 per cent. Three of these patients had no cardiac abnormality, one had angina pectoris, one had paroxysmal auricular tachycardia and five had cardiac disease of the congestive type.

OBSERVATIONS

Effect of Epinephrine on the Blood Pressure.—After the patient rested in the recumbent position for one-half hour measurements of the blood pressure and the heart rate were made at thirty second intervals until constant levels were obtained. The needle was then inserted in the vein. After the blood pressure and heart rate had returned to the resting level, epinephrine was administered at the rate of 0.25 cc. (1: 100,000 solution) per minute. The injection of epinephrine was continued at this rate until the blood pressure had maintained a stationary level for from two to five minutes. The rate of injection was then increased by increments of 0.25 cc. per minute, and the maximum effect of each new dose was determined in the same manner. The maximum response of the blood pressure to a given dose was usually obtained within two minutes after that rate of injection was started. The level of blood pressure remained relatively constant as long as the injection was continued at the same rate.

When the dose necessary to maintain the systolic blood pressure 20 mm. of mercury above the resting level was established, the injection was stopped. The amount of epinephrine necessary to increase and maintain the systolic blood pressure 20 mm. of mercury above the resting level proved to be the most satisfactory basis for estimating the effect of epinephrine on blood pressure. It was found early in the work that the administration of larger doses was unnecessary and was followed in some instances by a marked drop in the blood pressure after cessation of injection. In two patients, one with angina pectoris and one with paroxysmal auricular tachycardia, the systolic blood pressure was raised from an average of 190 mm. to approximately 270 mm. of mercury in an attempt to precipitate a typical attack. An attack was precipitated in the patient with angina pectoris; in both patients the systolic blood pressure following the cessation of injection of epinephrine fell to approximately 60 mm. of mercury, and the patients showed evidence of collapse from which they recovered several hours later. Untoward reactions following the subcutaneous or intramuscular injection of epinephrine have been observed by others.[10] Administration by the intravenous route allows one to control the concentration of circulating epinephrine. The danger of exceeding the patient's tolerance can be obviated by starting with a small dose and observing the reaction of the patient to gradually increasing doses.

During the injection of doses of epinephrine which increased the systolic blood pressure by 20 mm. of mercury the patients showed definite pallor and experienced palpitation; attacks of angina pectoris were not produced by these doses. After cessation of injection the systolic blood pressure fell within three minutes to the previous resting level, and a pronounced flushing of the skin, especially marked in the face, became apparent. In three instance, because of subjective discomfort, the injection of epinephrine was stopped before a 20 mm. increase in systolic blood pressure was produced.

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10. Cottrell, J. E., and Wood, F. C.: The Effect of Epinephrine in Angina Pectoris, Am. J. M. Sc. **181**:36, 1931. Katz, L. N.; Hamburger, W. W., and Lev, M.: The Diagnostic Value of Epinephrine in Angina Pectoris, Am. Heart J. **7**:371, 1932.

TABLE 1.—*Sensitivity to Epinephrine in Patients Studied at Different Levels of Basal Metabolic Rate as Estimated by the Amount of Epinephrine* Required to Raise the Systolic Blood Pressure Approximately 20 Mm. of Mercury*

Case	Diagnosis	Time of Study	Weight, Kg.	Basal Metabolic Rate, Percentage Deviation from Normal	Epinephrine Cc. per Minute of 1:100,000 Solution	Blood Pressure, Mm. of Mercury: Before Injection	Blood Pressure, Mm. of Mercury: During Injection	Heart Rate, Beats per Minute: Before Injection	Heart Rate, Beats per Minute: During Injection	Comment
		Patients Whose Basal Metabolic Rate Was Lowered by Total Ablation of Thyroid Gland								
1	Angina pectoris	Before operation	57	— 7	1.0	184/100	216/ 92	76	76	Anginal attacks at 57 to 96 trips†
		4 days after operation	..	—12	1.25	180/ 96	208/ 84	88	96	
		11 days after operation	55	—28	1.25	190/108	218/ 84	90	96	Anginal attack at 105 trips
		16 days after operation	55	—29	1.25	198/112	224/ 96	84	94	No anginal attack at 200 trips
		60 days after operation	57	—37	2.0	184/132	206/122	96	84	No anginal attack at 200 trips; clinical myxedema
2	Angina pectoris	Before operation	75	—10	0.85	200/100	226/118	66	74	Anginal attacks at 17 to 21 trips
		12 days after operation	73	—25	0.85	180/ 90	206/ 86	64	72	No angina clinically; trips not measured
		21 days after operation	73	—27	1.50	216/112	242/110	68	76	No angina clinically; trips not measured
3	Angina pectoris	Before operation	59	—15	1.0	128/ 88	152/ 80	68	84	Anginal attacks at 32 to 36 trips
		3 days after operation	..	—11	1.0	130/ 90	150/ 90	78	100	No anginal attack at 72 trips 7 days after operation (nerve relief)
		24 days after operation	59	—14	0.75	134/ 86	154/ 86	76	94	Anginal attack at 36 trips (thyroid, 3 grains daily)
		45 days after operation	59	—29	1.4	142/100	160/ 78	54	88	No anginal attack at 200 trips
		85 days after operation	62	—37	3.5	128/ 86	152/ 58	66	88	No anginal attack at 200 trips; clinical myxedema
		16 mos. after operation	..	—32	3.25	128/ 96	150/ 84	64	88	Anginal attacks at 32 trips; clinical myxedema
4	Congestive heart failure (auricular fibrillation)	Before operation	39	+20	0.5	118/ 90	132/ 90	78	116	Injection stopped because of subjective discomfort
		5 days after operation	..	— 6	0.5	114/ 90	128/ 86	86	106	Injection stopped because of subjective discomfort
		26 days after operation	40	—17	0.5	116/ 90	126/ 84	88	108	Injection stopped because of subjective discomfort
		38 days after operation	40	—27	0.5	116/ 94	126/ 90	78	105	Mild clinical myxedema; thyroid not necessary
5	Congestive heart failure	Before operation	61	—11	1.25	114/ 68	134/ 64	58	90	
		5 days after operation	..	—11	1.0	114/ 68	138/ 62	64	74	
		32 days after operation	65	—31	1.25	114/ 74	144/ 66	66	88	Mild clinical myxedema; thyroid not necessary
		109 days after operation	70	—33	1.25	102/ 70	120/ 66	56	60	Mild clinical myxedema; thyroid not necessary
		Patients Whose Basal Metabolic Rate Was Increased by Thyroid Medication								
6	Spontaneous myxedema	Before medication	54	—30	6.0	100/ 76	120/ 86	74	64	Marked clinical myxedema
		Thyroid, 2 grains daily	50	± 0	1.75	110/ 74	130/ 82	94	120	No myxedema
7	Diabetes mellitus, total ablation of thyroid	Before medication	58	—34	1.5	116/ 84	140/ 90	90	98	Marked clinical myxedema
		Thyroid, ¼ grain daily	58	—25	1.5	110/ 90	134/ 92	88	76	
		Thyroid, 5 grains daily	56	+ 8	0.75	110/ 68	136/ 68	120	132	No myxedema
		8 days after thyroid was omitted	56	— 5	0.75	104/ 70	126/ 68	88	110	

* Cubic centimeters per minute of 1:100,000 solution injected intravenously.

† Before operation in this patient some of the exercise tolerance tests were made during attacks of gout. At such times his exercise tolerance was diminished to approximately 60 trips, whereas when free from attacks of gout his tolerance was approximately 90 trips.

‡ The thyroid used throughout this work satisfied the requirements outlined in the "Pharmacopoeia of the United States," which were recently discussed in an article in The Journal of the American Medical Association (Means, J. H.: Therapeutics of the Thyroid, J. A. M. A. **105**:24 [July 6] 1935).

Systolic Blood Pressure: There was no relationship between the response of the systolic blood pressure to epinephrine and the type of cardiovascular disease or the level of the blood pressure while at rest (table 1). A progressive increase in the rate of flow of the solution of epinephrine was followed by a progressive increase in the systolic blood pressure. The dose of epinephrine necessary to cause a rise of approximately 20 mm. in the systolic blood pressure in a given subject on different days under the same conditions varied by no more than 0.25 cc. (1:100,000 solution) per minute. The sensitivity of different persons,

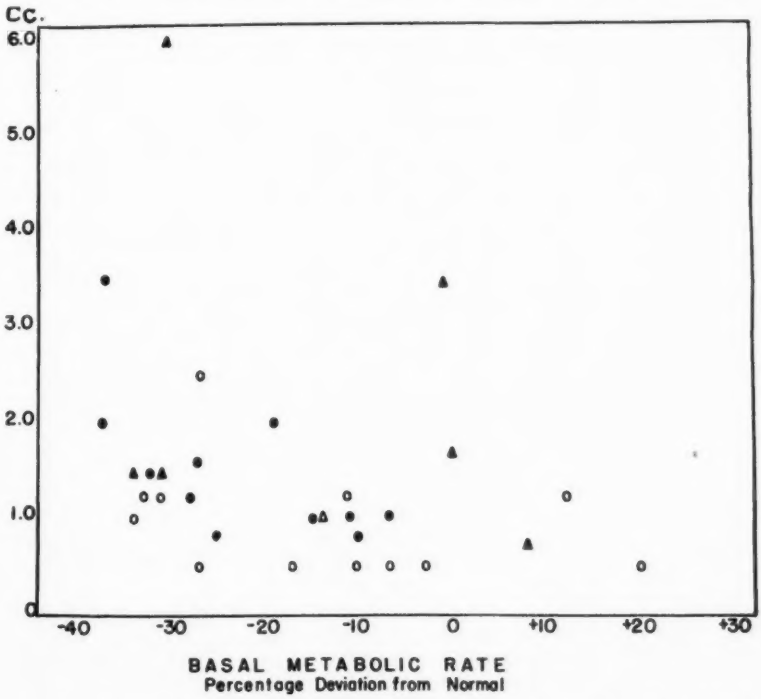

Chart 1.—The dose of epinephrine in cubic centimeters per minute of 1:100,000 solution required to raise the systolic blood pressure 20 mm. of mercury. The subjects studied included patients with various types of chronic cardiac disease (angina pectoris, indicated by the solid circle; congestive failure, indicated by the open circle, and paroxysmal auricular tachycardia, indicated by the open triangle) and subjects with no cardiac disease (indicated by the solid triangle).

however, varied considerably, whether expressed in terms of cubic centimeters of 1:100,000 solution per minute or in milligrams per kilogram per minute. The dose of epinephrine (1:100,000 solution) necessary to raise the systolic blood pressure 20 mm. of mercury varied from 0.5 cc. (0.00013 mg. per kilogram per minute) to 6 cc. (0.0011 mg. per kilogram per minute) in the different patients studied (table 1 and chart 1).

approximately 60 trips, whereas when free from attacks of gout no tolerance was approximately 30 trips.
† The thyroid used throughout this work satisfied the requirements outlined in the "Pharmacopoeia of the United States," which were recently discussed in an article in The Journal of The American Medical Association (Means, J. H.: Therapeutics of the Thyroid, J. A. M. A. 105:124 (July 6) 1935).

No definite correlation was evident between the response of the systolic blood pressure to epinephrine and basal metabolic rates between normal and minus 30 per cent; when, however, the basal metabolic rate was below minus 30 per cent and clinical evidences of severe myxedema were present some patients were definitely less sensitive to epinephrine (chart 1). In twenty-six of the thirty tests, regardless of the basal metabolic rate, from 0.5 to 2 cc. was required to raise the systolic blood pressure approximately 20 mm. of mercury. Of the four patients in whom more than 2 cc. was necessary three had basal metabolic rates between minus 29 and minus 37 per cent and showed clinical evidences of marked myxedema. It should be noted, however, that other patients with equally striking signs of myxedema and similarly reduced metabolic rates required only the usual dose of epinephrine.

In order to study more accurately possible changes in the response of the blood pressure to epinephrine at various metabolic levels, tests were repeatedly performed in seven patients when their basal metabolic rates were changed either by total thyroidectomy or by thyroid medication (table 1).

Three patients with angina pectoris were studied before and after total ablation of the thyroid gland. One of these patients (case 1, table 1) required 1 cc. of a 1:100,000 solution of epinephrine per minute to cause a rise in the systolic blood pressure of 32 mm. of mercury before operation when the basal metabolic rate was minus 7 per cent. Four days after the operation, when the metabolic rate had fallen to minus 12 per cent, there was no significant difference in the dosage necessary to cause a similar response in blood pressure, the variation from 1 to 1.25 cc. being within the limits of error of the method. Eleven and sixteen days after the operation, when the basal metabolic rates were minus 28 and minus 29 per cent, respectively, 1.25 cc. of epinephrine again caused the same response. A decrease in the basal metabolic rate from minus 7 to minus 29 per cent was thus accompanied by no appreciable change in the sensitivity to epinephrine. Sixty days later, when the basal metabolic rate became minus 37 per cent, the patient showed signs and symptoms of myxedema sufficient to make thyroid medication advisable. For the first time the patient was definitely less sensitive to epinephrine, 2 cc. being required to cause a rise in the systolic blood pressure of 22 mm. of mercury.

In another patient with angina pectoris (case 3, table 1) the basal metabolic rate was minus 15 per cent before the operation, and 1 cc. of epinephrine per minute caused a rise in the systolic blood pressure of 24 mm. of mercury. Three days after the operation the basal metabolic rate was minus 11 per cent and the response of the blood pressure to epinephrine was unchanged (table 1 and chart 2). For reasons stated later the basal metabolism of this patient was maintained during the next three weeks at the preoperative level by thyroid medication. The response to epinephrine was essentially unchanged (table 1). Thyroid medication was then discontinued; forty-five days after the operation the basal metabolic rate was minus 29 per cent and 1.4 cc. of epinephrine per minute induced a rise in the systolic pressure of 18 mm. of mercury. When the basal metabolic rate had become minus 37 per cent (eighty-five days after operation) signs and symptoms of myxedema severe enough to require thyroid medication were evident. A definite decrease in the sensitivity to epinephrine was evidenced for the first time, 3.5 cc. of epinephrine being required to induce a rise of 24 mm. of mercury in the systolic blood pressure (table 2 and chart 2). The results in the third patient with angina pectoris were in accord with these observations (table 1).

The two patients with congestive cardiac disease (cases 4 and 5, table 1) showed no change in response of the blood pressure to epinephrine at any time up to one month and three and a half months after total ablation of the thyroid gland. The basal metabolic rate in these two patients decreased from plus 20 per cent (case 4) and minus 11 per cent (case 5) to minus 27 and minus 33 per cent, respectively.

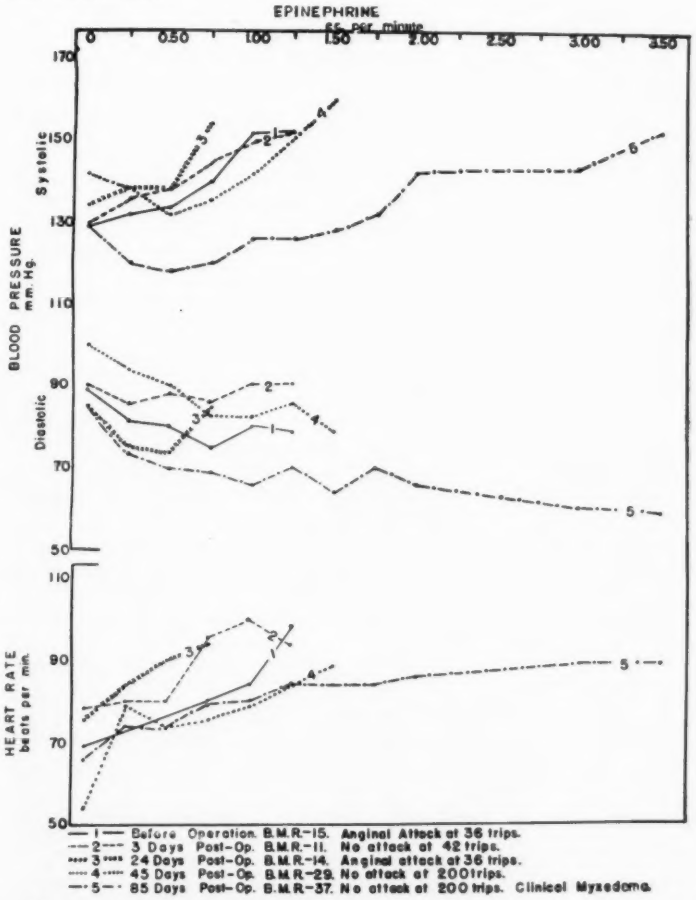

Chart 2 (case 3).—The response of the blood pressure and heart rate to epinephrine before operation and at intervals after operation. The results were appreciably different only when myxedema severe enough to necessitate thyroid medication developed (curve 5).

One patient with spontaneous myxedema (case 6, table 1) and marked symptoms required as much as 6 cc. of epinephrine to cause an increase of 20 mm. in the systolic blood pressure. When the basal metabolic rate was raised to normal 1.75 cc. caused the same response of the blood pressure. Another patient

TABLE 2.—*Oxygen Consumption and Respiratory Studies During Intravenous Administration of Epinephrine to Patients with Levels of Basal Metabolic Rate Varying from Plus 14 to Minus 35*

Case*	Diagnosis	Time of Study	Level of Basal Metabolism,† Percentage Deviation from Normal	Epinephrine, Cc. per Minute of 1:100,000 Solution	Blood Pressure, Mm. of Mercury		Oxygen Consumption		Respiratory Rate, Respirations per Minute		Respiratory Minute Volume, Liters per Minute	
					Before Injection	During Injection	Before Injection, Cc. per Minute	During Injection, Percentage Increase	Before Injection	During Injection	Before Injection	During Injection
2	Angina pectoris	Before total thyroidectomy	— 7	1.0	188/ 98	226/ 90	180	24	13	19	4.5	7.0
				0.5	.....	.....	190	12	15	18	4.5	6.0
		From 19 to 22 days after total thyroidectomy	—27	0.5	216/112	220/110	165	17	13	15	3.8	5.6
				1.5	216/112	242/110	160	34	15	20	5.0	6.2
3	Angina pectoris	Before total thyroidectomy	—15	1.0	128/ 88	152/ 80	165	22	16	21	5.5	10.0
				0.5	128/ 88	134/ 80	165	15	15	20	5.5	10.0
		From 46 to 49 days after total thyroidectomy	—29	1.5	142/100	160/ 78	145	17	15	18	5.5	10.0
				1.0	142/100	142/ 82	155	19	13	17	4.5	8.0
				0.5	142/100	132/ 90	140	21	16	18	6.6	9.5
6	Spontaneous myxedema	Before medication	—30‡	6.0	100/ 76	120/ 86	135	22	17	24	5.5	8.0
				2.0	100/ 76	98/ 76	130	22	15	19	4.5	5.5
		Thyroid, 2 grains daily	± 0	2.0	110/ 74	130/ 82	180	28	24	38	8.0	13.0
				1.0	110/ 74	128/ 84	170	16	25	38	10.5	16.0
				0.5	110/ 74	126/ 90	180	19	28	35	10.0	13.0
8	Congestive heart failure	Before total thyroidectomy	+14	1.5	240/120	282/102	180	20	20	24	5.5	7.5
				1.0	240/120	260/100	175	26	23	30	7.0	9.5
				0.5	240/120	256/100	185	19	20	25	6.0	9.0
9	Congestive heart failure	Before total thyroidectomy	± 0	0.5	190/118	216/100	165	27	18	23	6.0	7.0
				0.25	.....	.....	170	13	20	26	6.0	7.5
10	Congestive heart failure	Before total thyroidectomy	—12	0.5	112/ 72	130/ 58	180	15	16	19	5.0	7.0
				0.25	112/ 72	118/ 56	165	18	15	20	4.5	7.5
11	Congestive heart failure	Three months after total thyroidectomy	—35‡	2.0	102/ 86	150/ 80	145	16	8	11	3.5	5.0
				1.0	102/ 86	130/ 70	150	15	8	11	3.5	5.5
				0.5	102/ 86	114/ 76	160	11	6	8	3.5	4.5

* Cases 2, 3 and 6 of this table are those of the same number in table 1.
† The level of basal metabolism represents the average of many measurements of the basal metabolic rate made on days just preceding the tests with epinephrine.
‡ Clinical evidences of marked myxedema were present.

with diabetes mellitus and myxedema induced by total ablation of the thyroid gland (case 7, table 1) required 1.5 cc. of epinephrine when the basal metabolic rate was minus 34 and minus 25 per cent, and 0.75 cc. when the metabolic rate was brought to normal and the symptoms of myxedema relieved. In these two patients no tests were made when the basal metabolism was at intermediate levels.

The results in the patients studied show little or no change in the response of the systolic blood pressure to epinephrine as the basal metabolic rate varied from normal to approximately minus 30 per cent. When, however, signs and symptoms of severe myxedema developed with a basal metabolic rate of minus 30 per cent or lower some patients were less sensitive to epinephrine which was injected. This was evident in five patients, in two of whom (cases 3 and 6, table 1) the decrease in sensitivity was striking; in three others (cases 1, 2 and 7, table 1) the decreased sensitivity was relatively slight, being apparent only by comparison with the results obtained when symptoms of myxedema were not present. Although the response of the blood pressure was considerably decreased in cases 3 and 6 when the patients showed evidences of clinical myxedema, it is interesting to note that other patients with normal metabolic rates required a similar dose to evoke the same response (chart 1).

Diastolic Blood Pressure: With the doses of epinephrine which caused a rise in the systolic blood pressure of 20 mm. of mercury, the diastolic blood pressure usually showed either a slight decrease or no change (tables 1 and 2).[11] The response of the diastolic blood pressure during the injections of epinephrine was not related to the underlying cardiovascular condition, the resting blood pressure, the basal metabolic rate or the degree of clinical myxedema.

Effect of Epinephrine on the Heart Rate.—When the systolic blood pressure was increased 20 mm. of mercury the heart rate usually increased between 6 and 22 beats per minute (table 1). In approximately one-half the experiments the change in heart rate was less than 10 beats per minute. Whereas the systolic blood pressure increased progressively as the dose of epinephrine was increased, no constant relationship was observed between changes in the heart rate and the magnitude of dosage (tables 1 and 2).

Changes in heart rate were not related to the resting heart rate or to the state of the cardiovascular system. Patients with angina pectoris, congestive cardiac disease or paroxysmal auricular tachycardia, regardless of the underlying etiology, all responded in a similar manner. In one of five patients with auricular fibrillation, however, the heart rate increased 100 beats per minute with the dose of epinephrine which caused a rise in systolic blood pressure of 18 mm. of mercury. This unusual response may have been related to insufficient digitalization.

The heart rate at rest was essentially unchanged in the five patients after total thyroidectomy when the metabolic rate was lowered and clinical improvement was manifest (table 1). In the two patients with marked clinical myxedema who were studied during treatment with thyroid (cases 6 and 7, table 1) the basal heart rate was increased when the basal metabolic rate was raised to normal, and the rise in the ventricular rate during the injection of epinephrine was somewhat greater. Despite the normal basal metabolic rate in these two patients after thyroid medication they showed elevated basal pulse rates, flushing, excessive perspiration

11. In addition to the changes in blood pressure and heart rate which appear in tables 1 and 2, data on six other patients have been collected and show essentially the same findings.

and hyperactivity similar to that seen in patients with mild hyperthyroidism. This tendency of patients with myxedema to show evidence of mild hyperthyroidism after thyroid medication has been noted by others.[12]

No relationship between the basal metabolic rate and the response of the heart rate to epinephrine was evidenced in eighty-five tests made on seventeen subjects with basal metabolic levels from minus 37 to plus 20 per cent. In four patients changes in response of the heart rate were apparent when results in the same subjects were compared at different levels of basal metabolism (table 1). In cases 1 and 5 (table 1) when the basal metabolic rates were lowered to minus 33 and minus 37 per cent, respectively, the heart rate for the first time failed to respond appreciably to the injection of epinephrine, although the characteristic rise in blood pressure was elicited. In cases 6 and 7 (table 1) when the metabolism was raised to normal by thyroid, injection of epinephrine caused a greater increase in the heart rate.

Consumption of Oxygen and Respiration During Injection of Epinephrine.—The consumption of oxygen, the respiratory rate, the tidal air and the respiratory minute volume were studied in seven patients whose basal metabolic rate levels ranged from plus 14 to minus 35 per cent. Two patients who had angina pectoris were studied before and after total ablation of the thyroid gland; one patient with spontaneous myxedema was studied before and after thyroid therapy (table 2). All tests were performed with the patient in the postabsorptive state. The subjects had been accustomed to the Benedict-Roth metabolism apparatus. Control curves were obtained under basal conditions and also with the needle inserted in the vein. The results of these two measurements of the metabolic rate agreed satisfactorily with each other and with the basal metabolic rate measured on other days. During the course of recording the control curve, with the needle in place, the epinephrine was injected intravenously at the rate which had been found previously to cause an increment in systolic blood pressure of 20 mm. of mercury. On a subsequent date the test was repeated with a different dose of epinephrine. Measurements of blood pressure and pulse rate were made before and during the injection; the results were in accord with those found on other occasions when observations on the respiration and the consumption of oxygen had not been made.

The consumption of oxygen reached a maximum between one and two minutes after the injection of epinephrine at a given rate was begun and remained fixed at that level throughout the test. The doses of epinephrine utilized (from 0.25 cc. to 6 cc. per minute, table 2) caused increments from 11 to 34 per cent over the basal consumption of oxygen. The degree of increase showed no constant relationship to the dose of epinephrine, to the response of the systolic blood pressure or to the basal metabolic rate.

The intravenous administration of epinephrine invariably caused an appreciable increase in the respiratory rate and in the respiratory minute volume. The depth of respiration did not always increase. No relationship was apparent between the respiratory changes and the dose of epinephrine or the basal metabolism. The respiratory response of patients with congestive failure was not different from that of the other patients studied.

Response of the Blood Sugar.—The concentration of dextrose in the venous blood was measured immediately before the injection of epinephrine was begun and two

12. (*a*) Morris, R. M.; Witter, M. S., and Weiss, S.: An Unusual Sensitizing Action of Thyroid Substance on the Effect of Epinephrine in Man, Proc. Soc. Exper. Biol. & Med. **21**:149, 1923. (*b*) Means, J. H., and Richardson, E. P.: The Diagnosis and Treatment of Diseases of the Thyroid, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol. 4, p. 299.

minutes after the injection was stopped. A rise in the blood sugar content occurred during the administration of epinephrine, the average rise being about 10 mg. per hundred cubic centimeters. The extent of the rise of the blood sugar content was not related to the level of the basal metabolic rate or to the dose of epinephrine administered. In the patient with diabetes the blood sugar content did not show this characteristic increase, probably owing to the effect of insulin which had been administered several hours previously.

RELATIONSHIP BETWEEN SENSITIVITY TO EPINEPHRINE AND CLINICAL IMPROVEMENT AFTER TOTAL THYROIDECTOMY IN PATIENTS WITH CARDIAC DISEASE

In two patients with angina pectoris and in two patients with congestive failure an exceptional opportunity was afforded to study the relationship between clinical improvement and sensitivity to epinephrine. The findings in each subject at various times after operation were compared with those observed in the same subject before operation. In the two patients with angina pectoris the degree of clinical improvement was evaluated by the clinical course and by a standardized exercise tolerance test.[9]

In case 3 (table 1 and chart 2) the basal metabolism before operation was minus 15 per cent, and 1 cc. of a 1:100,000 solution of epinephrine per minute caused a rise in the systolic blood pressure of 24 mm. of mercury. Preoperatively daily attacks of angina occurred on exercise or on emotion and also while the patient was at rest in bed. Thirty-two trips under standardized conditions on the two step staircase regularly precipitated a characteristic attack of angina. During the first week after operation the patient was free from anginal attacks while at rest in bed, and 72 trips on the staircase failed to produce an anginal attack. However, the basal metabolic rate and the sensitivity to epinephrine remained essentially unchanged. This relief from pain immediately after operation, which is unrelated to changes in the metabolic rate or in sensitivity to epinephrine, has been extensively studied and has been shown to be due to interruption of sensory nerve impulses from the heart to the central nervous system at the time of operation.[13] To obviate the complicating effect of this early "nerve relief" in our studies of the relationship of changes in sensitivity to epinephrine to clinical improvement in this patient thyroid was administered in sufficient dosage to maintain the metabolic rate at the preoperative level until the temporary effect of interruption of nerve impulses had disappeared. Beginning with the seventeenth day after operation attacks of pain were again precipitated on exertion. At first, 55 trips were required, but the amount of exercise necessary to produce angina gradually decreased until on the twenty-fourth postoperative day typical anginal attacks were precipitated by the same amount of work that had induced attacks before operation. The administration of thyroid had maintained the basal metabolic rate at the preoperative level, and the sensitivity to epinephrine was still unchanged.

13. Weinstein, A. A.; Davis, D.; Berlin, D. D., and Blumgart, H. L.: The Mechanism of the Early Relief of Pain in Patients with Angina Pectoris and Congestive Failure After Total Ablation of the Normal Thyroid Gland, Am. J. M. Sc. **187**:753, 1934.

After the factor of relief of pain due to the effect of interruption of nerve impulses was no longer operative in this patient the relationship between various degrees of hypothyroidism and the sensitivity to epinephrine could be studied uncomplicated by other factors. Thyroid medication was then omitted. Forty-five days after operation the basal metabolic rate decreased to minus 29 per cent, and anginal attacks were not experienced spontaneously or after 200 trips on the staircase. A rise in systolic blood pressure of 18 mm. of mercury was produced by 1.4 cc. of epinephrine. Six weeks after this improvement was manifest, however, the basal metabolic rate had become minus 37 per cent and signs and symptoms of severe myxedema were evident. At this time the sensitivity to epinephrine was definitely decreased, 3.5 cc. being required to cause a rise of systolic blood pressure of 24 mm. of mercury (table 1 and chart 2).

Similar results were observed in case 1 by studies before and after operation (table 1). Preoperatively attacks of angina were produced after from 57 to 96 trips on the staircase. There was no evidence that the factor of early relief by the interruption of nerve impulses was of importance in this patient, for an attack of angina had been induced by 105 trips on the eleventh postoperative day. Sixteen days after total thyroidectomy when the basal metabolic rate had decreased to minus 29 per cent the patient for the first time was able to perform 200 trips without an anginal attack. The sensitivity to epinephrine was essentially the same as before the operation and at the time of two earlier postoperative tests made four days and eleven days after operation. Clinical improvement was maintained uninterruptedly. Nine weeks after the operation a slight decrease in sensitivity to epinephrine became evident. Clinical myxedema had developed, and the basal metabolic rate was minus 37 per cent.

In these two patients who were observed in the hospital the effect of early relief "nerve"[13] could be excluded, and the relationship of clinical improvement to altered sensitivity to epinephrine and to the degree of hypothyroidism could be studied with exceptional accuracy. Conspicuous clinical improvement was reflected by quantitative exercise tolerance tests and the clinical course at a time when no significant changes in the sensitivity to epinephrine could be detected. With the development of clinical myxedema the patients became relatively less sensitive to epinephrine; the clinical course was not favorably affected.

The two patients with congestive cardiac failure (cases 4 and 5, table 1) showed no change in sensitivity to epinephrine at any time up to one and three and one-half months after operation. Beginning one month after operation it was possible for them to undertake considerably more activity without precipitating any evidence of congestive failure than was possible before the operation. The absence of decreased sensitivity to epinephrine at the time when clinical improvement became manifest in these patients is in accord with our observations in the patients with angina pectoris.

These observations showed that relief from angina pectoris and congestive cardiac failure develops and persists at metabolic levels at which no significant changes can be detected in the sensitivity of the cardiovascular system to continuous intravenous injection of epinephrine. Such persistent improvement is rather to be related to the lessened work of the heart when hypothyroidism, as evidenced by a lowered basal metabolic rate, is induced.

COMMENT

Measurement of the sensitivity of patients to epinephrine before and after total ablation of the normal thyroid gland affords a direct approach to the study of the significance of changes in sensitivity to epinephrine in the improvement caused by this procedure.

In most investigations in which epinephrine has been administered the drug has been given subcutaneously or intramuscularly. When so given the drug acts first on the local blood vessels, and the rate of absorption is consequently irregular and beyond control. At times the response is delayed and prolonged,[3] at other times a dangerous reaction and even coronary thrombosis may occur [10] because of unduly rapid absorption. The nature of the response varies in different persons and even may vary considerably from day to day in the same person. The intravenous injection of epinephrine under the controlled conditions outlined previously is relatively safe and offers many advantages. The amount introduced is immediately physiologically active and can be accurately controlled. If any untoward symptoms or signs develop injection can be interrupted and the effects soon terminated. Administration of the same solution to the same persons on different days produces extraordinarily uniform responses, and so the effect of variation in but one physiologic factor such as the metabolic level can be accurately studied.

The results presented earlier indicate that the intravenous administration of epinephrine to human subjects is followed by a definite and characteristic increase in the systolic blood pressure, heart rate, oxygen consumption of the body, rate and depth of respiration and blood sugar content. The response of the blood pressure signifies the effect of epinephrine on the vasomotor system; the changes in ventricular rate indicate the effect of epinephrine on the sinus node, and changes in the consumption of oxygen, the effect of epinephrine on the tissues of the body in general. In addition to the factors studied in this investigation other effects of epinephrine are recognized, such as the ability to produce extra ventricular systoles.[14] The changes which we have reported in this paper, however, are those which are generally accepted as indexes of epinephrine activity and are those which are closely linked with the physiologic activity of the cardiovascular system in man. The effect of epinephrine on the cardiac minute volume output of man will be the subject of a forthcoming communication.

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14. Nahum, L. H., and Hoff, H. E.: The Mechanism of Sudden Death in Experimental Acute Benzol Poisoning, J. Pharmacol. & Exper. Therap. **50**:336, 1934. Nathanson, M.: A Method for the Study of the Rhythmic Property of the Human Heart, Proc. Soc. Exper. Biol. & Med. **30**:967, 1933.

The systolic blood pressure was found to be the most delicate index of the patient's sensitivity to epinephrine and was the only measurement which showed a progressive rise as the dose of epinephrine was increased. The rise of the systolic blood pressure in our subjects with and without cardiovascular disease was similar to that observed by Weinberg [5] and Cori and Buckwald,[2c] who also gave the drug by continuous intravenous drip to normal human subjects. The amount of epinephrine necessary to influence the blood pressure apparently varies in different persons. We have found no evidence, however, that patients with angina pectoris or valvular cardiac disease are more sensitive than normal persons. Petersen and Levinson [15] found that patients with a cardiovascular renal condition reacted to epinephrine in a manner similar to that of normal persons.

The heart rate of human beings with a normal basal metabolic rate is only slightly increased by the action of epinephrine. This is shown by the work of Goetsch,[16] Peabody, Sturgis, Tompkins and Wearn,[17] Sandiford,[18] Rogers,[19] Hinton,[20] Blumgart [21] and Cori and Buckwald [2c] as well as by the observations recorded in this communication. These findings are contrary to the results obtained with the use of the denervated cat's heart. As Cannon [22] has shown, the "denervated cat's heart is exquisitely sensitive to variations in the adrenin content of the circulating blood." This is brought about by two factors: 1. Following interruption of sympathetic nerve pathways the response of epinephrine becomes abnormally enhanced.[23] 2. In preparing the denervated heart

15. Petersen, W. F., and Levinson, S. A.: The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, Arch. Path. **9**:243 (Jan., pt. 2) 1930.

16. Goetsch, E.: Studies on Disorders of the Thyroid Gland. Hypersensitiveness Test with Especial Reference to "Diffuse Adenomatosis" of the Thyroid Gland, Endocrinology **4**:389, 1920.

17. Peabody, F. W.; Sturgis, C. C.; Tompkins, B. M., and Wearn, J. T.: Epinephrine Hypersensitiveness and Its Relation to Hyperthyroidism, Am. J. M. Sc. **161**:508, 1921.

18. Sandiford, I.: The Effect of the Subcutaneous Injection of Adrenalin Chloride on the Heat Production, Blood Pressure and Pulse Rate in Man, Am. J. Physiol. **51**:407, 1920.

19. Rogers, L.: The Adrenalin Test for Thyrotoxicosis, Lancet **2**:970, 1928.

20. Hinton, J. W.: The Adrenalin Test and Cholesterol Determinations in the Diagnosis of Borderline Hyperthyroidism, Am. J. M. Sc. **180**:681, 1930.

21. Blumgart, H. L.: The Circulatory Response to Epinephrine, Libman Anniv. Vol. **1**:215, 1932.

22. Cannon, W. B.: Studies on the Conditions of Activity in Endocrine Organs: XXVII. Evidence that Medulliadrenal Secretion is Not Continuous, Am. J. Physiol. **98**:450, 1931.

23. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil Dilatation by Adrenalin, Am. J. Physiol. **11**:218, 1904. Elliott, T. R.: The Action of Adrenalin, J. Physiol. **32**:439, 1905. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man, Am. J. Physiol. **107**:529, 1934.

care is taken to sever all the nerve pathways which normally inhibit the action of epinephrine. The operative procedure, therefore, makes the denervated heart preparation an extremely delicate indicator of the presence of circulating epinephrine. This preparation, however, does not give insight into the action of epinephrine on the normal intact cardiovascular system.

The consumption of oxygen by man is increased by injections of epinephrine, as shown by our observations and those of Sandiford,[18] Castex and Schteingart,[24] Blumgart [21] and Cori and Buckwald.[2c] In our experience with graded dosages of epinephrine no close relationship between the dosage and the increment in the oxygen consumption was found. The maximum increase which we observed was 34 per cent. This observation is in general accord with the findings of others who gave the drug subcutaneously, intramuscularly or intravenously.[25] Our observations (table 2) and those of Castex and Schteingart [24] have shown that the increase in consumption of oxygen caused by epinephrine is the same in persons with hypothyroidism as in persons whose basal metabolic rate is normal. The observations of Sandiford [18] are in general accord with these findings, although two of her patients with basal metabolic rates of minus 30 and minus 40 per cent showed a somewhat lessened response.

The results obtained in this investigation are somewhat different than might be expected from a survey of the literature on the interrelation of the thyroid and the adrenal glands and the effect of these glands on the cardiovascular system. The chief difficulties which attend the application of previous knowledge to the interrelationship of these glands in man and their influence on clinical cardiovascular conditions arise from the following factors: (1) the variation in reaction of different species to epinephrine; (2) the hazards of applying observations made on animals to cardiac conditions which occur only in man; (3) the necessity of extirpating all thyroid tissue to insure the development of hypothyroidism, and (4) the technical difficulties attending the removal of all thyroid tissue.

The marked differences in the response of different species to epinephrine [2] and the inadvisability of applying the results noted in experimental animals to the interpretation of disordered cardiovascular states in intact human beings have been commented on earlier in this communication. Although removal of the thyroid gland might be

24. Castex, M. R., and Schteingart, M.: Action de l'adrenaline sur la depense calorique, la calcémie et la potassémie chez l'homme normal au atteint de troubles thyroidiens, Compt. rend. Soc. de biol. **99**:1649, 1928.

25. Sandiford.[18] Castex and Schteingart.[24] Blumgart.[21] Cori and Buckwalt.[2c]

expected to lead to hypothyroidism, evidence exists that even an extraordinarily small amount of thyroid tissue which may not be removed frequently undergoes hypertrophy and maintains a normal metabolic rate both in animals and in man. Halsted [26] found that complete removal of all thyroid tissue followed by reimplantation of a minute bit of thyroid into the rectus abdominis muscle was followed by hypertrophy of the transplanted fragment and the absence of signs of hypothyroidism. The earlier failures of one of us (H. L. B.)[27] and those of others [28] to induce persistent hypothyroidism by maximal subtotal removal of the thyroid gland demonstrate the necessity of removing every vestige of the normal thyroid tissue. The necessity of total ablation of the thyroid to insure the permanently lowered metabolic rate of hypothyroidism is in contrast to the effectiveness of subtotal removal of the abnormal gland in lowering the metabolic rate of thyrotoxicosis to normal. The frequent occurrence of aberrant thyroid tissue in animals [29] is often the cause of the absence of hypothyroidism even after the entire gland itself is removed. The absence of measurements of the metabolic rate in some investigations makes it impossible to learn the degree to which this factor operates.

After complete extirpation of the thyroid in man, hypothyroidism develops gradually, the basal metabolic rate becoming appreciably lowered; not earlier than the end of the first week, and frequently not before the sixth to the eighth week, are markedly low levels reached. In animals some experiments have been performed immediately or within a few hours after thyroidectomy when the metabolic rate was presumably not lowered and before hypothyroidism could have developed.

The clinical improvement which follows total ablation of the thyroid gland is independent of changes in the sensitivity of epinephrine. Results of the present investigation demonstrate that the sensitivity of the cardiovascular system to epinephrine in our patients as reflected

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26. Halsted, W. S.: Report of a Dog Maintained in Good Health by a Parathyroid Autograft Approximately One-Fourth of a Millimeter in Diameter, and Comments on the Development of the Operation for Graves' Disease as Influenced by the Results of Experiments on Animals, J. Exper. Med. **15**:205, 1912.

27. Friedman, H. F., and Blumgart, H. L.: Treatment of Chronic Heart Disease by Lowering the Metabolic Rate: IV. The Necessity for Total Ablation of the Thyroid, J. A. M. A. **102**:17 (Jan. 6) 1934.

28. Rose, E.: Malignant Hypertensive Vascular Disease Simulating Hyperthyroidism: Clinical Course Following Maximal Subtotal Thyroidectomy, M. Clin. North America **16**:261, 1932. Deutrebande, L.: Personal communication to the authors.

29. Marine, D., and Lenhart, C. H.: The Influence of Glands with Internal Secretions on the Respiratory Exchange: I. Effect of Subcutaneous Injection of Adrenalin on Normal and Thyroidectomized Rabbits, Am. J. Physiol. **54**:248, 1920.

by the response of the blood pressure and ventricular rate is the same before operation, within a few days after operation and later in the postoperative course when, according to our practice, a moderate degree of hypothyroidism is maintained. These results are not in complete accord with those of Eppinger and Levine,[30] who injected epinephrine intramuscularly and found either the same response or a somewhat lessened response of the blood pressure and pulse rate a few days after operation. If a decreased sensitivity to epinephrine were an important factor in conferring relief on patients after total thyroidectomy a relationship between these two phenomena should be apparent. Clinical improvement in our patients was evident, however, long before any demonstrable change in sensitivity to epinephrine occurred, and many patients showed persistent clinical improvement without showing decreased sensitivity to epinephrine. Observations which have been presented in an earlier communication [13] demonstrate that the absence of pain which has been observed soon after operation under conditions of rest [31] or exercise (case 3)[13] or after injections of epinephrine [30] is due to the interruption of sensory impulses from the heart to the central nervous system. After the effect of the early interruption of nerve pathways is no longer apparent clinical relief persists without any change in sensitivity to epinephrine (cases 1 and 3).

No significant change in the response to epinephrine was observed in our cases when the basal metabolic level varied from the normal to approximately minus 30 per cent. When the basal metabolism was lower than minus 30 per cent and signs and symptoms of clinical myxedema became manifest the response of the blood pressure and heart rate was in some instances lessened and in other instances unchanged. These findings are in accord with the observations of Sandiford.[18] In addition, Sandiford found a somewhat decreased increment in the oxygen consumption after the subcutaneous injection of epinephrine in two patients with spontaneous myxedema and basal metabolic rates of minus 30 and minus 40 per cent.

Several patients with angina pectoris who failed to obtain complete relief from pain when the basal metabolism was maintained at a level of approximately minus 30 per cent showed additional relief when the basal metabolism was allowed to decrease to lower levels at which some of the distressing symptoms of myxedema were experienced. Although a decreased sensitivity to epinephrine is not evident in all patients with the metabolic rates at such levels, this factor may contribute to the

30. Eppinger, E. C., and Levine, S. A.: Effect of Total Thyroidectomy on Response to Adrenalin, Proc. Soc. Exper. Biol. & Med. **31**:485, 1934.

31. Blumgart, Riseman, Davis and Berlin.[1] Weinstein, Davis, Berlin and Blumgart.[13]

additional improvement witnessed in some patients with metabolic levels below minus 30 per cent.

One might consider that although the sensitivity of the cardiovascular system is unchanged the amounts of epinephrine produced by the adrenal glands after total thyroidectomy conceivably might be reduced and the heart subjected to less intense stimuli. Unfortunately, quantitative tests for measuring the concentration of circulating epinephrine in man are not available. Certain facts, however, make it appear most unlikely that a diminished production of epinephrine postoperatively, either at rest or on exertion, plays a significant rôle in the improvement observed in our patients. If after operation a lessened amount of epinephrine were produced at rest one would expect the heart rate and blood pressure during rest to be definitely decreased, and larger amounts of epinephrine injected intravenously should be required to cause the systolic blood pressure and the heart rate to reach the same heights as before operation. This has not been our experience. Similarly, there is no evidence that the production of epinephrine on exercise is diminished after operation. If a lesser secretion of epinephrine occurred on exercise after thyroidectomy the characteristic indexes of circulating epinephrine should be less evident after thyroidectomy. Standardized exercise by the same patient before and after operation has revealed that the response of the heart rate and blood pressure was usually the same or even greater.[32]

The amounts of epinephrine which were injected in this investigation were presumably as large as or greater than amounts secreted under clinical conditions. With the doses usually employed pallor, tremor, palpitation and other signs of the action of epinephrine were manifest, and with slightly greater doses toxic and, at times, dangerous, reactions were encountered.

It is to be noted that although the response to epinephrine may not be changed appreciably when the basal metabolism falls to approximately minus 30 per cent following thyroidectomy a definitely increased response of the blood pressure, heart rate or consumption of oxygen may be obtained when the metabolism is raised by the administration of thyroid.[12] Further, myxedematous patients, after the basal metabolic rate has been brought to normal by thyroid medication, may show signs and symptoms of mild hyperthyroidism (cases 6 and 7).[12a]

The effect on the metabolic rate is not the only or even the primary action of the active principle of the thyroid gland. Di-nitrophenol and di-nitro-ortho-cresol also are powerful metabolic stimulants, but there is no evidence that they possess any of the other "hormonal" actions of

32. Riseman, J. E. F.: The Relation of the Systolic Blood Pressure and Heart Rate to Attacks of Angina Pectoris Precipitated by Effort, to be published.

thyroid secretion.[33] In the absence of such artificial substances and such unphysiologic states the metabolic rate still affords the best single index of the degree of hypothyroidism. For the discussion in this paper of the sensitivity to epinephrine at different levels of hypothyroidism we have utilized both the metabolic rate and the clinical manifestations of myxedema as indexes of the hypothyroid state. That the thyroid and the adrenal glands have important interrelationships is not negated by our work. The level of hypothyroidism at which changes in this relationship may become evident is, however, below that maintained in our patients after thyroidectomy and so is of little or no significance in contributing to the therapeutic results of total thyroidectomy.

SUMMARY AND CONCLUSIONS

Studies of the sensitivity of the cardiovascular system of man to injections of epinephrine before and after total thyroidectomy are presented.

Three aspects of the physiologic action of epinephrine have been studied: (1) the sensitivity to epinephrine injected intravenously in patients with normal cardiovascular systems, angina pectoris or chronic cardiac failure; (2) the sensitivity to epinephrine of patients with various levels of basal metabolism, and (3) the rôle played by sensitivity to epinephrine in the improvement which occurs following total ablation of the thyroid gland in patients with angina pectoris or chronic heart disease.

Dilute solutions of epinephrine of known concentrations were injected by constant intravenous drip, and the responses of the blood pressure, heart rate, respiratory rate and depth, consumption of oxygen and blood sugar content were measured. Eighty-six studies were made in seventeen subjects.

The intravenous administration of epinephrine was followed by a definite and characteristic increase in the systolic blood pressure, heart rate, consumption of oxygen of the body, rate and depth of respiration and blood sugar content. The changes in diastolic blood pressure were variable and not great.

The responses to a given amount of epinephrine injected intravenously were strikingly similar when repeated measurements were made in a given subject under controlled conditions. The responses varied from person to person.

33. Dodds, E. C., and Robertson, J. D.: The Clinical Applications of Dinitro-Ortho-Cresol, Lancet **2**:1197, 1933. Cutting, W. C., and Tainter, M. L.: Comparative Effects of Dinitrophenol and Thyroxin on Tadpole Metamorphosis, Proc. Soc. Exper. Biol. & Med. **31**:97, 1933. Tainter, M. L.; Stockton, A. B., and Cutting, W. C.: Use of Dinitrophenol in Obesity and Relative Conditions, J. A. M. A. **101**:1472 (Nov. 4) 1933. Means, J. H., and Lerman, S.: The Action of Iodine in Thyrotoxicosis. ibid. **104**:969 (March 23) 1935. Unpublished observations on patients treated by total thyroidectomy.

The response of the systolic blood pressure was closely related to the rate of injection of epinephrine and was found to be the most valuable single index of the patient's sensitivity to epinephrine. The changes in heart rate, diastolic blood pressure, consumption of oxygen and measurements of respiration were not as directly related to the dose of epinephrine.

Patients with angina pectoris and those with congestive heart failure were not more sensitive to epinephrine than patients with no evidences of cardiovascular pathologic changes.

The sensitivity to epinephrine as measured by the aforementioned generally accepted indexes remained unchanged after total thyroidectomy so long as the basal metabolic rate was not lower than minus 30 per cent and the patient was free from distressing symptoms of myxedema.

When marked myxedema developed and the basal metabolic rate decreased below minus 30 per cent, a decreased response of the blood pressure and the heart rate to epinephrine became manifest in some instances.

The results of the present investigation show that the clinical improvement which followed total ablation of the normal thyroid gland is independent of any changes in the sensitivity to epinephrine, no alteration in the response to epinephrine being evident at the levels of hyperthyroidism maintained in our patients after operation.

Observations are presented which provide additional evidence that the relief from pain experienced by patients with angina pectoris immediately after total thyroidectomy, when there is no change in the basal metabolic rate or in sensitivity to epinephrine, is due to the interruption of sensory impulses from the heart to the central nervous system.

CIRCULATORY CHANGES IN ANGINA PECTORIS

AN EXPERIMENTAL STUDY

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The great majority of clinicians and investigators are now agreed on the essential pathologic physiology of angina pectoris, namely, that the attacks represent a transitory relative ischemia of a portion of the myocardium. There is, however, considerable doubt as to the mechanism of the production of the ischemia. Two fundamental possibilities present themselves: The supply of normal blood is inadequate for the needs of the heart muscle, or the composition of the blood is faulty, preventing a proper interchange of oxygen and metabolites. The latter possibility probably applies in only relatively few cases. The maintenance of an adequate supply of blood to the myocardium depends on two variable factors the demands of the myocardium and the ability of the blood vessels to meet this demand.

The factors which determine the ability of the blood vessels to meet the vascular demands of the myocardium are (1) the ability of the vessels to dilate as the demands of the heart muscle increase and (2) active vasoconstriction of the coronary arteries with or without an increase in the demands of the heart muscle. There is some doubt as to whether there is active vasoconstriction of the coronary arteries in man, although certain observations [1] suggest that it occurs. However, even if coronary spasm can and does occur as an etiologic factor in certain cases of angina pectoris, there are many cases of this disorder in which the postmortem condition of the coronary arteries is such as to make it highly improbable that the attacks of pain are due to transitory changes in the caliber of these vessels. In these cases it would seem more reasonable to suppose that the attacks are due to an increase in the demands of the heart muscle in the presence of an inability of the coronary vessels to meet this increased demand, because a narrowing or a rigidity prevents adequate vasodilatation.

In this group of cases one should look to the factors which increase the vascular demands of the heart muscle if one is seeking the precipitating cause of the individual attacks of pain. Such factors would be those which increase the heart rate or increase the vascular resistance

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1. (*a*) Barbour, H. G.: The Constricting Influence of Adrenalin upon the Human Coronary Arteries, J. Exper. Med. **15**:404, 1912. (*b*) Anrep, G. W.: The Regulation of the Coronary Circulation, Physiol. Rev. **6**:596, 1926.

against which the heart must pump. It is a familiar observation that the usual conditions which bring on an attack of angina pectoris—physical exertion, exposure to cold and emotional upsets—are conditions generally associated with a rise in blood pressure and an increase in the heart rate. Moreover, the clinical observation that the attack of angina is frequently associated with a rise in blood pressure or heart rate, or both, has been well established. The fact, however, that this finding has not been invariable has led to a misinterpretation of the significance of these circulatory changes. It has been generally assumed that these changes are secondary phenomena caused by the pain and anxiety incident on the attack. However, as Christian [2] pointed out in commenting on the occurrence of attacks in which the pulse rate and blood pressure are found to be normal,

> . . . of course it is possible that both changes occurred at or prior to the onset of the attack and had disappeared by the time some one could observe the pulse and blood pressure.

In recent years more careful observations have been made of the circulatory changes during the attack of angina pectoris. Wood and Wolferth [3] reported observations on the blood pressure of fifteen patients during the attack of pain and found it definitely elevated in thirteen. In one of the two remaining cases, the blood pressure was observed to be 140 systolic and 100 diastolic, as compared with a previous reading of 150 systolic and 100 diastolic, but ten minutes after the attack it was found to have fallen to 125 systolic and 100 diastolic. Levine and Ernstene [4] recently reported observations on twenty-three patients during spontaneous attacks and found that the blood pressure was definitely elevated in all of them. They stated the belief that the elevation is not due to the pain and suggested that the rise in blood pressure may, on the other hand, be the cause of the attack.

> . . . the fact that in the subsidence of the attack, pressure levels need not go hand in hand with the disappearance of the pain, does not dismiss the possibility that the onset of the attack was actually produced by the increased pressure.

Levine stated that a fall in blood pressure during anginal attacks must be rare, and when it occurs one should suspect that an attack of coronary thrombosis is occurring, or that the pain is not anginal in character. In a careful clinical study of anginal attacks induced by exercise, Wayne and Laplace [5] found an associated elevation of blood

2. Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1928, vol. 3, p. 244.

3. Wood, F. C., and Wolferth, C. C.: Angina Pectoris, Arch. Int. Med. **47**: 339 (March) 1931.

4. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attacks of Angina Pectoris, Am. Heart J. **8**:323, 1933.

5. Wayne, E. J., and Laplace, L. B.: Observations on Angina of Effort, Clin. Sc. **1**:103, 1933.

pressure and pulse rate. They agreed with Levine that the circulatory changes are more likely to be the cause than the result of the paroxysm. However, they concluded that the increased heart rate is more important than the elevated blood pressure in causing the attack, because they found the duration of the distress to be more closely correlated with the former.

A new approach to the problem of angina pectoris was provided by the consistent production of a definite pain response in dogs, mechanical interference with the coronary blood flow being employed. This was first demonstrated by Singer,[6] in 1926, and was corroborated and enlarged on by Sutton and Lueth,[7] who by an ingenious series of experiments showed that the pain response is due solely to the interference with the coronary blood flow and not to any adventitious factors incidental to the experimental procedure. These observations have since been corroborated by Pearcy, Priest and Van Allen [8] and by White, Garrey and Atkins.[9] White and his associates successfully used this response as a means of testing the effectiveness of various surgical procedures to interrupt the sensory pathways of the heart. The experimental procedure described by Sutton and Lueth consists in passing a suture about the anterior descending branch of the left coronary artery and bringing it out of the chest through a glass tube, about which the pericardium and thoracic wall are tightly closed. When the animal has fully recovered from the anesthesia, relatively slight traction on the coronary suture produces an almost immediate and unmistakable pain response, which ceases on the release of the traction.

Sutton and Lueth made observations of the blood pressure during this mechanical interference with the coronary blood flow with the animal under anesthesia and found that the blood pressure always showed a moderate fall. Wood and Wolferth [3] made the same observation; in attempting to explain this discrepancy as compared with the rise in blood pressure generally seen in clinical anginal attacks, they stated:

> The objection raised against the coronary hypothesis by these observations is not insurmountable. The blood pressure phenomena appearing during an experiment on an anesthetized animal cannot be expected to be reproduced exactly in a

6. Singer, R.: Experimentelle Studien über die Schmerzempfindlichkeit des Herzens und der grossen Gefässe und ihre Beziehung zur Angina Pectoris, Wien. Arch. f. inn. Med. **12**:193, 1926; **13**:157, 1927.

7. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827 (June) 1930.

8. Pearcy, J. F.; Priest, W. S., and Van Allen, C. M.: Pain Due to Temporary Occlusion of the Coronary Arteries in Dogs, Am. Heart J. **4**:390, 1929.

9. White, J. C.; Garrey, W. E., and Atkins, J. A.: Cardiac Innervation, Arch. Surg. **26**:765 (May) 1933.

conscious man. The pressor reflexes set up by the pain of an anginal attack seem adequate to counteract a moderate fall of blood pressure due to a temporary myocardial ischemia.

None of these investigators have recorded blood pressure observations during the production of the pain response in the unanesthetized dog by this method. The following experimental study was undertaken in the hope of shedding light on the rôle of changes in the heart rate and blood pressure in attacks of angina pectoris.

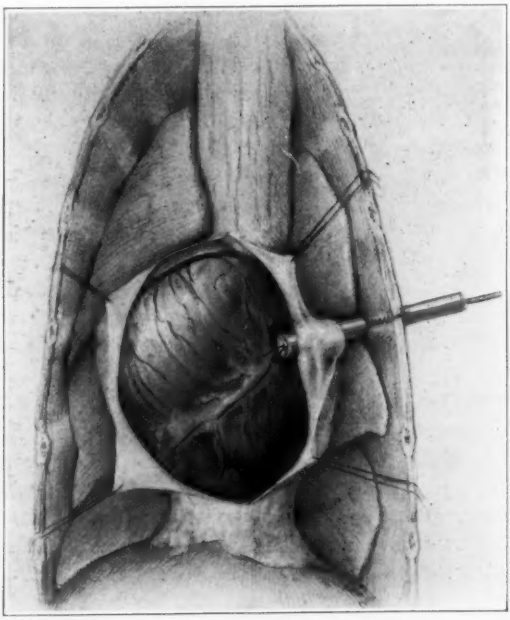

Fig. 1.—Drawing of a postmortem specimen, showing the coronary suture in situ.

METHOD

The procedure was essentially the same as that described by Sutton and Lueth. Under intratracheal ether anesthesia the left fifth rib was resected from the sternum to the midaxilla, and the pleura was opened. The pericardium was incised over the tip of the left auricle, which was displaced upward, exposing the proximal segment of the anterior descending branch of the left coronary vessels. An "E" silk suture was passed about the coronary vessels at this point by means of a blunt aneurysm needle after a small nick in the epicardium had been made to facilitate introduction. The suture was brought out of the chest through a flanged glass tube about which the pericardium and thoracic wall were tightly

closed, care being taken to remove the pneumothorax (fig. 1). The femoral artery was cannulated for blood pressure tracings, and provision was made for recording the respirations by means of a tambour. The ether was then withdrawn, the intratracheal tube removed and the animal allowed to recover from the anesthesia. From thirty to ninety minutes later the animal became sufficiently alert to respond in the typical manner to traction on the coronary suture. In all of the cases the inclusion of the coronary artery by the suture was corroborated by postmortem dissection. In some of the experiments the arterial cannula was withdrawn, the animal was removed from the operating table for recovery, and no effort was made to record the blood pressure during the subsequent observations. When epinephrine was used, the dilutions were made with distilled water just before the test. The

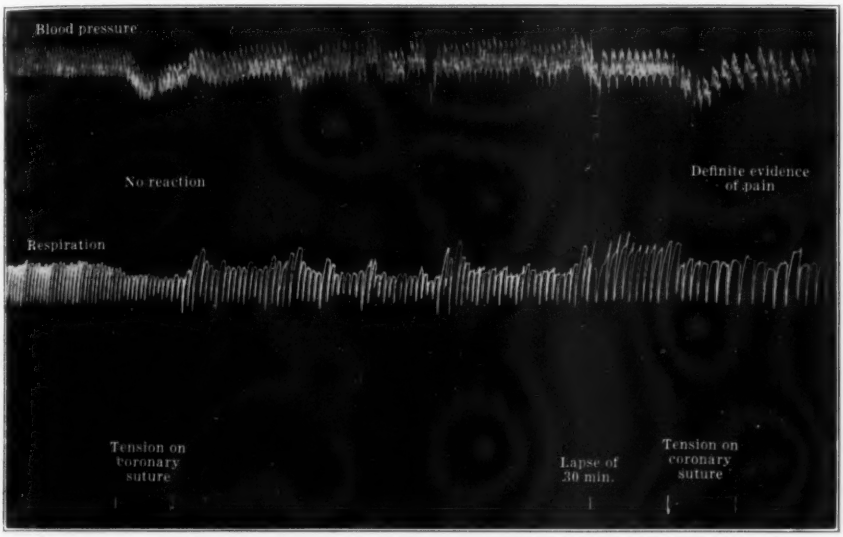

Fig. 2.—Tracing from dog C9, showing the blood pressure reaction to traction on the coronary suture before and after recovery from anesthesia.

dosages of epinephrine were measured accurately in a tuberculin syringe, and the rate of injection was carefully timed.

OBSERVATIONS

Effect of Experimental Angina Pectoris on the Blood Pressure.—The effect of interfering with the coronary blood flow in four dogs was observed before and after recovery from the anesthesia. While the dog was still anesthetized a slight fall in blood pressure was invariably noted. After recovery from the anesthesia, when traction on the coronary suture evoked a definite pain reaction, the blood pressure still showed a slight fall in most cases (figs. 2 and 3). There was no

appreciable variation in a few experiments, and in several a slight rise was observed (fig. 4). In no case did a significant rise of blood pressure occur (table). A definite variation in the heart rate occurred during traction on the coronary suture, but this was always a slowing, which was particularly marked when the traction was first applied and which frequently caused a sharp transitory fall in blood pressure. No change was noted in this reaction after recovery from the anesthesia; there was therefore no evidence that the discomfort tended to cause tachycardia.

The fact that a rise in blood pressure was never observed during traction on the coronary suture while the animal was under anesthesia,

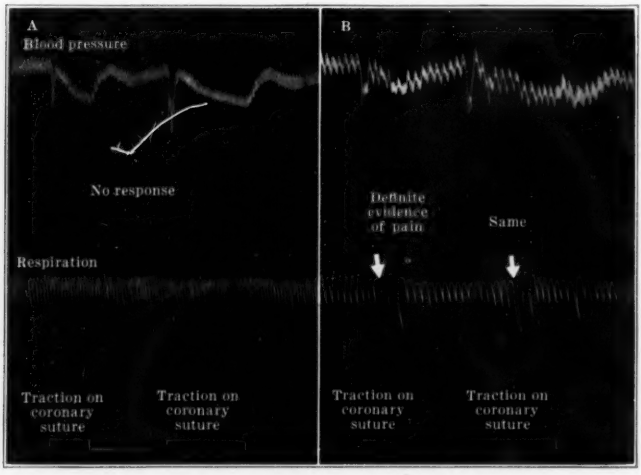

Fig. 3.—Tracing from dog C6, showing the blood pressure reaction to traction on the coronary suture (*A*) before recovery and (*B*) after recovery.

whereas a slight rise was occasionally seen when the test was repeated after recovery, suggests that the pain reaction may in several instances have caused this rise. However, there was no relation between the degree of the objective response of the dog and these minor variations in the blood pressure reaction, and the rise was so slight when it occurred that I believe that it cannot account for the rather striking elevation frequently seen in clinical attacks of angina. Moreover, I accidentally had the opportunity to observe the blood pressure reaction to pain of a different origin when on two occasions a small amount of 20 per cent citrate solution used in the arterial cannula flowed back into the artery, causing an unexpected pain reaction of considerable severity requiring reetherization. There was no rise in blood pressure

with even this severe reaction (fig. 5). In this connection it is interesting to recall the clinical observation by Levine [4] that the blood pressure remained unaltered during two severe attacks of renal colic in a patient who was subject to attacks of angina pectoris.

Effect of Elevation in the Blood Pressure on the Production of Experimental Angina Pectoris.—The production of a pain response by Sutton and Lueth's method depends on a mechanical constriction of the coronary vessels. This reproduces the mechanism in clinical angina pectoris only so far as one assumes an active vasoconstriction as a cause of the attacks. This factor has not been proved and is highly questionable in many cases. Therefore I endeavored to precipitate the

Change in Blood Pressure with Traction on the Coronary Suture

Dog	Initial Pressure, Mm. Hg	Observations Before Recovery from Anesthesia, Mm. Hg	Observations After Recovery and in Presence of Pain Reaction, Mm. Hg
C 6	130	Fall, 18 Fall, 16	Fall, 20 Fall, 28 Fall, 10 Fall, 14 Fall, 6
C 380	144	Fall, 6 Fall, 4	Rise, 8 No change Rise, 6 Fall, 8
C 9	148	Fall, 18 Fall, 10	No change No change Rise, 6 Fall, 6 Rise, 10
C 10	140	Fall, 16	Fall, 18 Fall, 10 Fall, 16 Fall, 10

typical pain reaction in dogs by increasing the myocardial demands and keeping the coronary blood flow relatively constant. This was successfully accomplished by maintaining a steady subminimal traction [10] on the coronary suture by means of weights suspended over pulleys (fig. 6) and then sharply increasing the circulatory load on the heart by injecting epinephrine into the femoral vein.

Dog C 364.—The animal was given 30 mg. of morphine and ether intratracheally on Nov. 29, 1933. The left fifth rib was resected, and the suture placed around the anterior descending branch of the left coronary vessels and brought out through the glass tube. The wound was closed.

Four hours later the dog was active and alert. Traction on the coronary suture produced an immediate response characterized by a stiffening of the fore-

10. The term subminimal traction is used to describe the pull which is just less than that required to elicit the discomfort reaction.

legs and increased respiration and restlessness. An intravenous injection of 0.5 cc. of a 1:10,000 solution of epinephrine caused no evidence of discomfort. A constant traction was now maintained on the coronary suture by means of weights

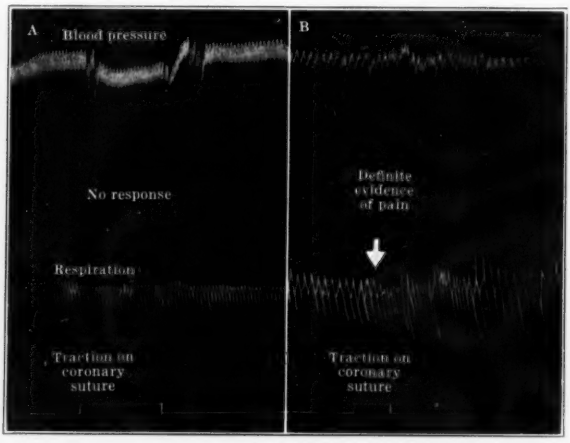

Fig. 4.—Tracing from dog C12, showing the blood pressure reaction to traction on the coronary suture (*A*) before recovery and (*B*) after recovery.

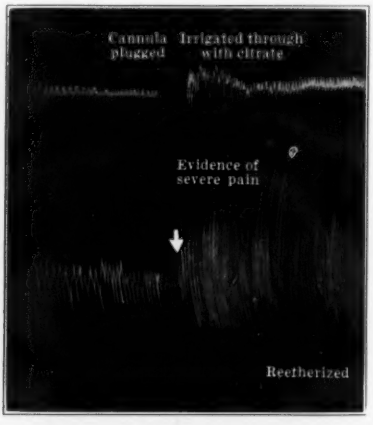

Fig. 5.—Tracing from dog C9, showing no appreciable change in the blood pressure in the presence of a severe pain response.

(100 Gm.) suspended over pulleys, the tension being so adjusted as to be less than that required to produce pain. The aforementioned dose of epinephrine was now repeated and within from ten to fifteen seconds there was a sudden pain reaction, similar, though more severe, than that produced previously by direct

traction on the coronary suture. The pain was relieved by a release of the traction. After a rest of five minutes, during which epinephrine alone again produced no evidence of discomfort, this procedure was repeated; the constant moderate traction was maintained for from three to four minutes without discomfort, following which the same dose of epinephrine was again followed almost immediately by the unmistakable pain reaction.

Dog C 360.—On Dec. 3, 1933, this animal was prepared like dog C 364. Four hours later it was completely recovered and alert. The femoral artery was cannulated under local anesthesia, and tracings of blood pressure and respiration were recorded on a smoked drum. Traction on the coronary artery evoked the typical response with increased respiratory rate but no significant change in blood pressure. Five-tenths cubic centimeter of a 1:10,000 solution of epinephrine administered

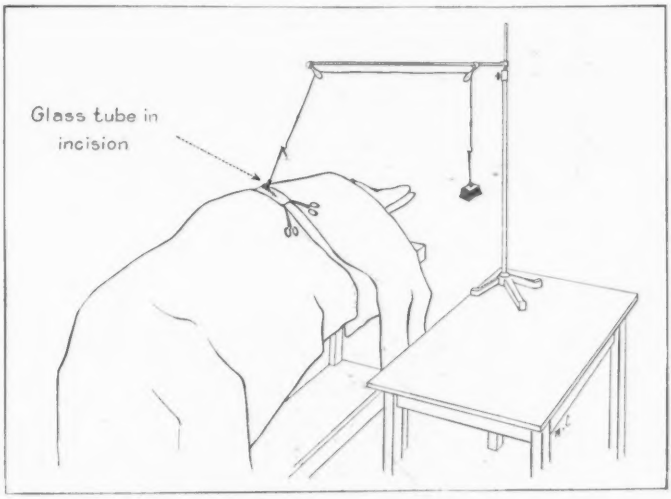

Fig. 6.—Diagram of the apparatus for maintaining constant traction on the coronary suture.

intravenously caused a sharp rise in blood pressure but no evidence of discomfort and no respiratory change. A constant traction of 100 Gm. was applied to the coronary suture without evidence of discomfort. Injection of the same dose of epinephrine was now followed by definite evidence of pain with an increase in respiratory rate, relieved by release of the pull (fig. 7). The same procedure was repeated after ten minutes, again producing the definite pain response.

Dog C 9.—On Jan. 12, 1934, the animal was prepared as were the other animals. It was alert and responsive forty minutes after the cessation of ether. A typical response was elicited by traction on the coronary suture. Two-tenths cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously caused a rise in blood pressure but no discomfort. Constant traction of 100 Gm. was applied to the suture without discomfort. The same dose of epinephrine was then

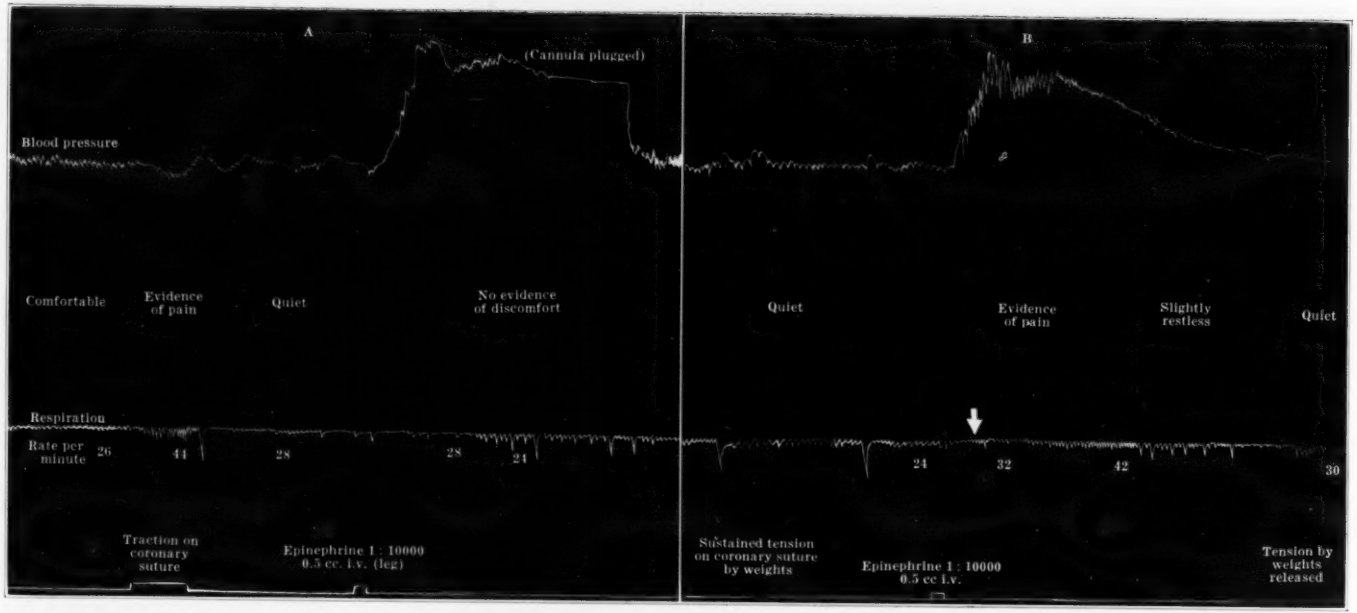

Fig. 7.—The tracing from dog C360. *A* shows no response to epinephrine alone, and *B*, a positive response to epinephrine with subminimal traction on the coronary suture.

repeated, and a definite pain reaction (fig. 8) was obtained. The injection of epinephrine was repeated without the traction, and again there was not the slightest evidence of discomfort.

Dog C 12.—On Feb. 26, 1934, the animal was prepared like the others. A prompt, typical reaction to traction on the coronary suture was elicited thirty minutes after the cessation of ether. One-tenth cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously produced a satisfactory rise in blood pressure without evidence of discomfort. Constant traction of 120 Gm. was applied to the coronary suture without discomfort. The injection of epinephrine was now repeated with a definite pain response at the height of the vasopressor reaction (fig. 9).

Dog C 29.—On March 20, 1934, the animal was prepared as usual. The vasopressor response to various doses of epinephrine was determined, following which

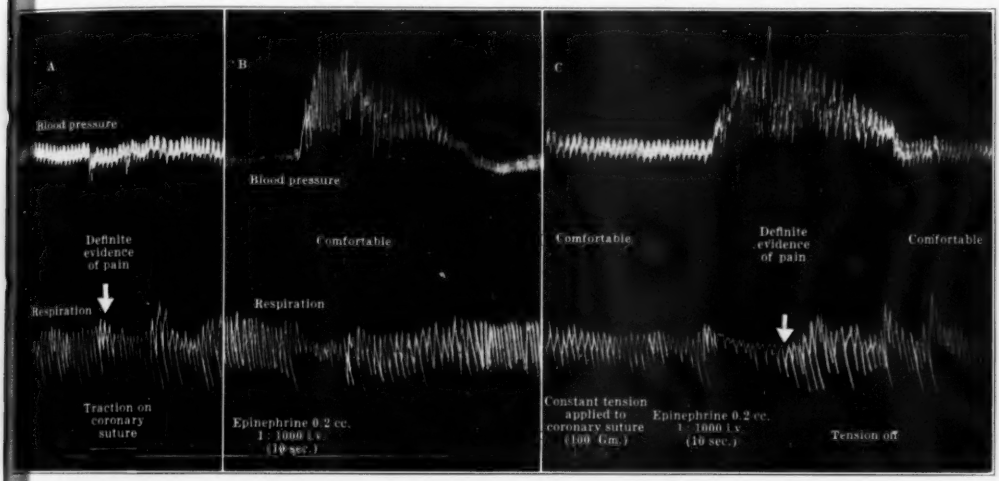

Fig. 8.—Tracing from dog C9. *A* shows the typical reaction to traction on the coronary suture; *B*, absence of response to epinephrine alone, and *C*, a typical response to epinephrine, with subminimal traction on the coronary suture.

the arterial cannula was removed and the animal allowed to recover from the anesthesia. Observations were made one-half hour later, only the respirations being recorded. Traction on the coronary suture produced the typical response. Four-tenths cubic centimeter of a 1:10,000 solution of epinephrine administered intravenously was given without discomfort. A constant traction of 100 Gm. was applied to the coronary suture without causing discomfort. Increasing doses of epinephrine were then injected without a reaction until 0.2 cc. of a 1:10,000 solution was reached. This injection was followed in thirty seconds by the definite typical reaction which subsided spontaneously after forty-five seconds, although the traction was maintained. The onset and duration of the response were found to correspond fairly closely to the previously determined vasopressor reaction to the same dose of epinephrine. A larger dose of epinephrine (0.4 cc. of a 1:10,000 solution) was followed by a definitely severer reaction, which was relieved by

cessation of the traction. As a final control, 0.5 cc. of a 1:10,000 solution of epinephrine was injected without the constant traction, and no response was obtained (fig. 10).

Dog C 288.—On March 21, 1934, the animal was prepared by the usual procedure. The vasopressor effect of varying doses of epinephrine was determined, the arterial cannula was removed and the animal allowed to recover. Four hours later it responded in the typical fashion to traction on the coronary suture. One-tenth cubic centimeter of a 1:1,000 solution of epinephrine administered intravenously caused no discomfort. Constant tension of 100 Gm. was applied to the coronary suture and maintained without causing discomfort. The same dose of epinephrine was then followed in fifteen seconds by the typical reaction.

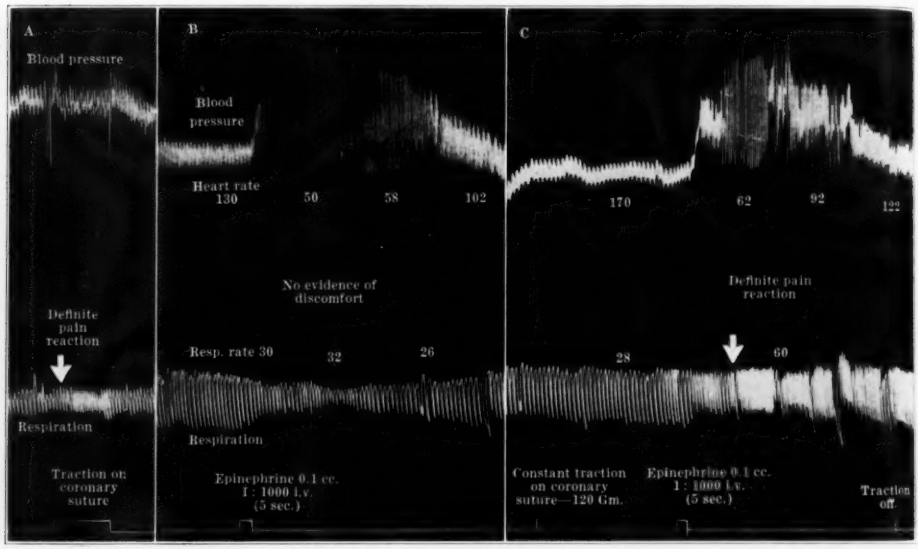

Fig. 9.—Tracing from dog C12. *A* shows the typical reaction to traction on the coronary suture; *B*, absence of response to epinephrine alone, and *C*, a typical response to the same dose of epinephrine, with subminimal traction on the coronary suture.

I was unsuccessful in seven experiments. In three of these pain in the leg inadvertently produced by the citrate solution [11] necessitated immediate reetherization and termination of the observations. Two dogs were too restless for accurate observations, and in two dogs no reaction was produced by subminimal traction and epinephrine, in spite of good cooperation. The failure in these two experiments is not sur-

11. A rather strong solution of sodium citrate (20 per cent) had been used. This was later abandoned for a sodium sulphate solution, one-half saturated.

prising in view of the difficulties involved in establishing a constant constriction of the coronary vessels, which of itself is not sufficient to cause pain but which so obstructs the coronary blood flow as to cause an insufficient supply of blood when the demands of the myocardium are suddenly increased.

Three possible mechanisms are to be considered in attempting to explain the production of pain by the injection of epinephrine, as described earlier: 1. There is an active vasoconstriction of the coronary artery which, superimposed on the already existing subminimal mechanical constriction, is sufficient to produce the myocardial ischemia and the consequent pain response. This factor may be dismissed in view of the general agreement among physiologists that epinephrine dilates rather than constricts the coronary arteries in the dog.[1b] 2. There is a resulting tachycardia which increases the vascular demands of the myocardium, and these demands cannot be adequately supplied in view of the mechanical constricton of the coronary vessels. This factor did not obtain in these experiments, however, as the dosage of epinephrine used caused a slowing of the heart, which was at times marked (fig. 9), but never an acceleration. 3. The rise in blood pressure increases the work of the heart, thus increasing the vascular demands of the myocardium, which are not adequately supplied. This appears to be the most probable explanation, for in none of the experiments could the pain reaction be produced by a dosage of epinephrine insufficient to cause a fairly good rise in blood-pressure (fig. 10). It seemed advisable, however, in view of the recent observations by Wayne and Laplace,[5] to try to produce this pain reaction by accelerating the heart rate without raising the blood pressure; experiments were therefore undertaken with this in view.

Effect of Increasing the Heart Rate on the Production of Experimental Angina Pectoris.—I first attempted to increase the heart rate by sectioning the vagi, which had been previously mobilized, but this was found to disturb the dog too much for subsequent accurate observations. Atropine was found to be satisfactory, as it causes a marked tachycardia which occurs within a few seconds after intravenous injection but no elevation of blood pressure (fig. 11). However, the tachycardia, which is due to paralysis of the vagus, persists for a number of hours; therefore the observation of the effect of suddenly increasing the heart rate in the presence of a subminimal traction on the coronary suture could be carried out only once during a given experiment.

Dog C 8.—On March 23, 1934, the animal was prepared as in previous experiments, and the vasopressor response to varying dosages of epinephrine was determined while the dog was still under anesthesia. The cannula was removed, and the dog was allowed to recover. Four hours later, a prompt, typical response

was obtained by pulling on the coronary suture. A constant traction of 100 Gm. was applied to the suture without evidence of discomfort. Increasing doses of epinephrine were then injected without response, until 0.2 cc. of a 1 : 1,000 solution was reached, which produced the typical reaction relieved by releasing the pull. After a rest of five minutes the same subminimal constant traction was again applied and then both 0.1 cc. of a 1 : 1,000 solution and 0.2 cc. of a 1 : 1,000 solution failed to precipitate the pain reaction. With the traction still in place, 0.54 mg. of atropine sulphate dissolved in 4 cc. of distilled water was given intravenously, followed by a sudden increase in the heart rate from 128 to 200 per minute, coming on within fifteen seconds after the injection. There was no indication of discom-

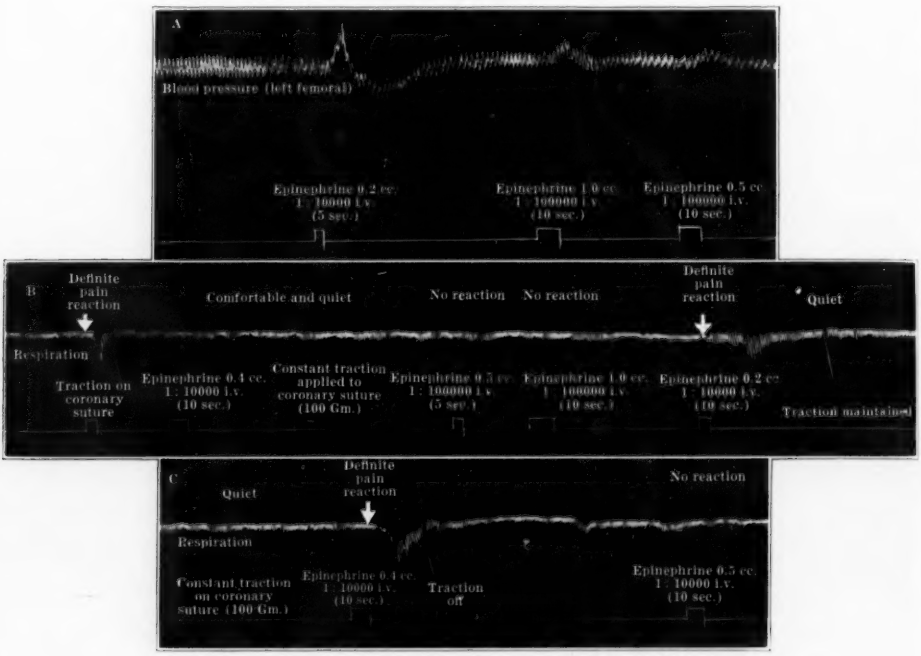
A
Blood pressure (left femoral)
Epinephrine 0.2 cc. 1 : 10000 i.v. (5 sec.)
Epinephrine 1.0 cc. 1 : 100000 i.v. (10 sec.)
Epinephrine 0.5 cc. 1 : 100000 i.v. (10 sec.)
B
Definite pain reaction
Comfortable and quiet
No reaction
No reaction
Definite pain reaction
Quiet
Respiration
Traction on coronary suture
Epinephrine 0.4 cc. 1 : 10000 i.v. (10 sec.)
Constant traction applied to coronary suture (100 Gm.)
Epinephrine 0.5 cc. 1 : 100000 i.v. (5 sec.)
Epinephrine 1.0 cc. 1 : 100000 i.v. (10 sec.)
Epinephrine 0.2 cc. 1 : 10000 i.v. (10 sec.)
Traction maintained
C
Quiet
Definite pain reaction
No reaction
Respiration
Constant traction on coronary suture (100 Gm.)
Epinephrine 0.4 cc. 1 : 10000 i.v. (10 sec.)
Traction off
Epinephrine 0.5 cc. 1 : 10000 i.v. (10 sec.)

Fig. 10.—Tracing from dog C29. *A* shows the vasopressor response to various doses of epinephrine; *B*, the typical reaction to traction on the coronary suture, failure to respond to epinephrine alone, maintenance of constant subminimal traction without discomfort and a positive reaction to epinephrine in the presence of this constant traction, and *C*, a more severe reaction to a larger dose of epinephrine in the presence of the same constant traction, immediate relief by release of traction and absence of reaction after a final control injection of epinephrine.

fort. However, the dose of 0.1 cc. of a 1 : 1,000 solution of epinephrine, which twice previously had failed to produce the response, was now followed by a marked and typical reaction (fig. 12).

Dog C 70.—On March 28, 1934, the animal was prepared according to the usual procedure. Four hours later it responded in the usual manner to traction

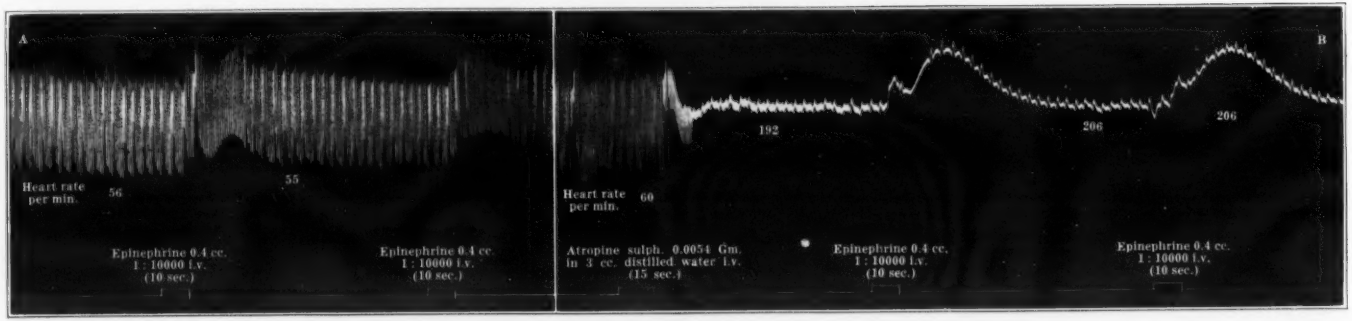
A
Heart rate per min. 56
55
Epinephrine 0.4 cc. 1 : 10000 I.v. (10 sec.)
Epinephrine 0.4 cc. 1 : 10000 I.v. (10 sec.)
B
192
206
206
Heart rate per min. 60
Atropine sulph. 0.0054 Gm. in 3 cc. distilled water I.v. (15 sec.)
Epinephrine 0.4 cc. 1 : 10000 I.v. (10 sec.)
Epinephrine 0.4 cc. 1 : 10000 I.v. (10 sec.)

Fig. 11.—Tracing from dog C31, which received morphine anesthesia, showing the vasopressor effect of epinephrine (*A*) before atropinization and (*B*) after atropinization. Note the prompt response of the tachycardia to atropine.

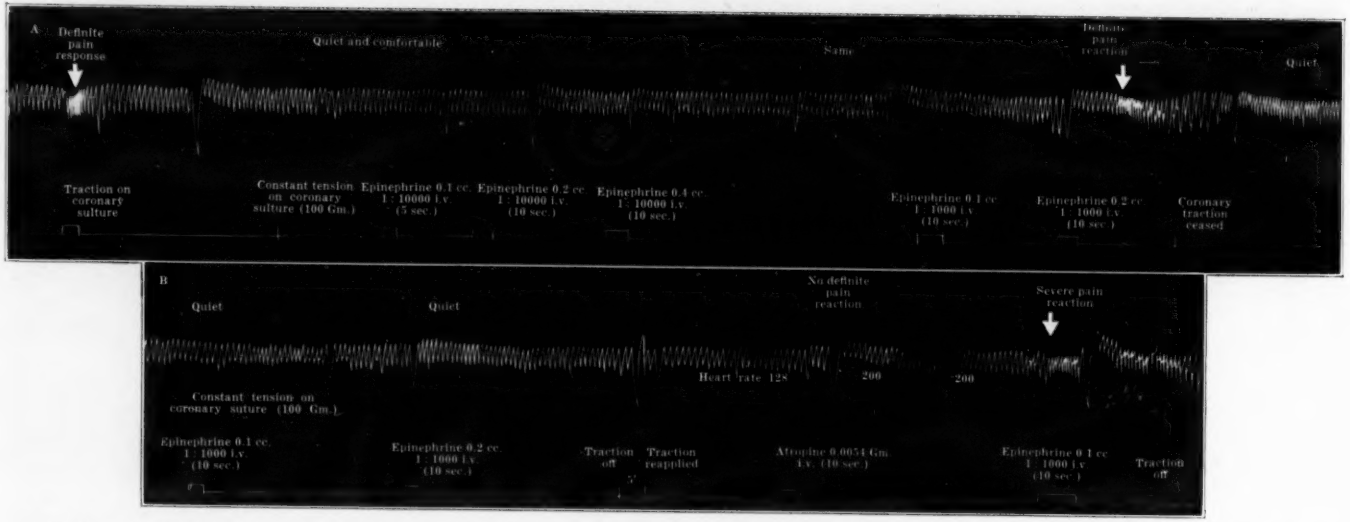
A
Definite pain response
Quiet and comfortable
Same
Definite pain reaction
Quiet
Traction on coronary suture
Constant tension on coronary suture (100 Gm.)
Epinephrine 0.1 cc. 1 : 10000 i.v. (5 sec.)
Epinephrine 0.2 cc. 1 : 10000 i.v. (10 sec.)
Epinephrine 0.4 cc. 1 : 10000 i.v. (10 sec.)
Epinephrine 0.1 cc. 1 : 1000 i.v. (10 sec.)
Epinephrine 0.2 cc. 1 : 1000 i.v. (10 sec.)
Coronary traction ceased
B
Quiet
Quiet
No definite pain reaction
Severe pain reaction
Heart rate 128
200
200
Constant tension on coronary suture (100 Gm.)
Epinephrine 0.1 cc. 1 : 1000 i.v. (10 sec.)
Epinephrine 0.2 cc. 1 : 1000 i.v. (10 sec.)
Traction off
Traction reapplied
Atropine 0.0054 Gm. i.v. (10 sec.)
Epinephrine 0.1 cc. 1 : 1000 i.v. (10 sec.)
Traction off

Fig. 12.—Tracing from dog C8. *A* shows the typical reaction to traction on the coronary suture, the maintenance of constant traction without discomfort, a positive reaction to epinephrine when a satisfactory vasopressor dose was reached and relief from discomfort on cessation of the traction, and *B*, no response to atropine in the presence of the subminimal traction and an increased reaction to epinephrine after atropinization.

on the coronary suture. Four-tenths cubic centimeter of a 1: 10,000 solution of epinephrine was injected without disturbing the animal. A constant traction of 50 Gm. was applied to the suture without evidence of discomfort. This dose of epinephrine was followed by the typical reaction of moderate severity. With the subminimal pull still in effect, the heart rate was increased from 104 to 172 per minute by the intravenous injection of 0.54 mg. of atropine, the tachycardia occurring within twenty seconds but without any evidence of discomfort. The epinephrine was now repeated in the same dosage as before and was followed by a typical reaction, definitely more severe than before the onset of the tachycardia (fig. 13).

Increasing the heart rate by atropine in the presence of a subminimal traction on the coronary suture failed to precipitate the pain reaction in the foregoing experiments, whereas an elevation of the blood pressure by epinephrine in the same dogs and with the same degree of mechanical constriction of the coronary vessels produced the typical response. However, it was found that after the tachycardia had been established, a smaller dosage of epinephrine produced the reaction, and that the

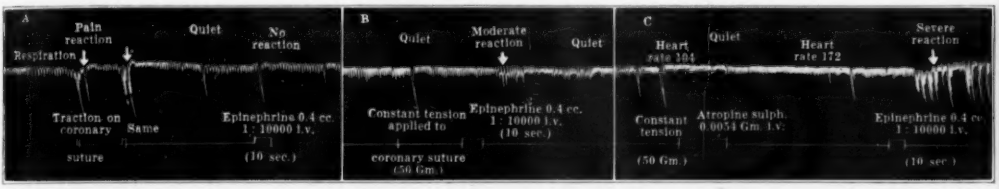

Fig. 13.—Tracing from dog C70. *A* shows a typical response to traction on the coronary suture, with no reaction to epinephrine alone; *B*, a positive reaction to epinephrine with subminimal traction on the suture, and *C*, no reaction to atropine with a subminimal traction on the suture, and increased reaction to epinephrine after atropinization.

reaction to a given effective dose of epinephrine was definitely more severe than previously.[12]

COMMENT

My observations on the effect of mechanical interference with the coronary blood flow in unanesthetized dogs are in accord with those of previous observers. There is a constant typical reaction which without doubt signifies pain. A graphic record of this reaction can be made only by noting changes in the respiratory tracing. This is, however, by no means an accurate record of the reaction as observed at the time

12. The increased effectiveness of epinephrine after atropinization may be due to (1) the fact that the vascular demands of the myocardium are already increased by the tachycardia or (2) the fact that the vasopressor response to epinephrine is somewhat greater with the vagus paralyzed (fig. 11), presumably owing to abolition of the depressor reflex.

of the experiment, for on several occasions an unmistakable pain response with whining and stiffening of the forelegs was observed with no change in the respirations (figs. 2 and 7). The important observation in the foregoing studies, therefore, is the note made at the time of the experiment as to the objective reaction of the animal. The changes in the respiratory tracings are merely confirmatory and in addition serve to record the time relations of the response. When the respiration is altered with the pain reaction, and this is the rule, I have found that an acceleration is a more accurate indication than is an increase in amplitude. In this connection I wish to emphasize the fact that in no case was the animal allowed to suffer unnecessarily. As soon as the definite typical response had occurred, the traction was immediately terminated, with prompt relief of the discomfort. It was found unnecessary to carry the stimulus beyond the point at which a moderate degree of discomfort was produced.

These experimental observations lend support to the clinical concept that the elevation of blood pressure frequently observed in angina pectoris is more likely the cause than the result of the attack. The tachycardia may also play a similar rôle, although I have not been able to demonstrate this in my experiments with animals. The fact that these circulatory changes may precipitate attacks in certain cases of angina pectoris does not mean that they are the important factors in all cases of this disorder.

SUMMARY

Experimental evidence is presented to show that in the dog cardiac pain produced by mechanical constriction of the coronary vessels does not cause a significant rise in blood pressure. On the other hand, the pain response can be precipitated by suddenly raising the blood pressure in the presence of a subminimal constriction of the coronary vessels.

ACUTE CARDIAC INFARCTION INVOLVING ANTERIOR AND POSTERIOR SURFACES OF LEFT VENTRICLE

ELECTROCARDIOGRAPHIC CHARACTERISTICS

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AND
FRANCIS CLARK WOOD, M.D.
WITH THE COLLABORATION OF SAMUEL BELLET, M.D.
PHILADELPHIA

Twenty of our cases of acute coronary occlusion have come to necropsy during the past three years. In every instance the location of the infarct, predicted on the basis of the electrocardiogram, has been confirmed.[1] This would indicate that when chest leads are used as well as limb leads the position of an acute infarct can be determined with considerable accuracy. The localizing signs of typical anterior and typical posterior lesions have been described in a previous paper.[2] Moreover, the prognostic difference between the groups, mentioned in that paper, has been confirmed by further observations.[1]

Certain factors may confuse the observer in attempting to locate the lesion: 1. The infarct may occur in some unusual position, as in the lateral wall of the left ventricle or in the right ventricle. The localizing signs of such lesions are not definitely established as yet. 2. The patient may have had a previous cardiac infarct. However, in our experience this has not prevented the localization of a recent lesion.[3] 3. Ten cases have occurred in our series of 104 in which contradictory signs have appeared. In this group there have been electrocardiographic indications of acute lesions in both the anterior and the posterior wall of the left ventricle. In some cases the tracing has suggested that the main lesion was anterior (case 1), and in others, that the main infarct was posterior (case 2). Two of the 10 cases have come to necropsy. The pathologic examination in each instance revealed a lesion involving part

From the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

1. Wolferth, C. C.; Wood, F. C.; Bellet, S., and Edeiken, J.: The Electrocardiographic Diagnosis of Coronary Occlusion with Chest Leads, Tr. A. Am. Physicians **49**:223, 1934.

2. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Diagnosis of Coronary Occlusion: Further Observations on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933.

3. Wood, Bellet, McMillan and Wolferth,[2] cases 3 and 33.

of both the anterior and the posterior wall of the left ventricle. Consequently, in this paper, an attempt has been made to analyze the electrocardiographic findings in this group and to outline the signs of acute anteroposterior cardiac infarction.

CASE 1.—J. L., a white man aged 52, had noticed undue dyspnea on effort since January 1933. On Dec. 11, 1933, at 10 p. m., while playing with his children, he experienced an intense deep-seated pain beneath the sternum which spread to the precordium and radiated to the left shoulder. A feeling of suffocation accompanied the pain. He became nauseated and subsequently vomited Morphine gave some relief, but his suffering continued through the night and the next morning. He was admitted to the Hospital of the University of Pennsylvania in the service of Dr. Alfred Stengel at noon on December 12.

Examination at that time revealed: temperature, 98 F.; pulse rate, 90, and respiratory rate, 28. The blood pressure was 120 systolic and 75 diastolic. The patient appeared acutely ill. He was somewhat irrational, orthopneic and cyanotic. No abnormalities of the heart sounds were noted. There were many râles at the base of the right lung. The leukocyte count was 20,000.

The next day the temperature rose to 101 F.; the heart sounds became more distant. The blood pressure dropped to 100 systolic and 65 diastolic. The pain persisted with occasional remissions. On December 14 it subsided. On December 17 the temperature was normal and the leukocyte count was 11,800. On December 21 fever recurred, and pain in the right side of the chest appeared. On December 26 at 7:30 a. m. the patient suddenly collapsed and died.

Necropsy was performed by Dr. John Parsons on December 26. The left anterior descending coronary artery was obstructed by a recent thrombus 1.5 cm. from its origin. The other coronary arteries were relatively free from sclerosis. None were stenosed or obstructed. The circumflex branch of the left coronary artery was unusually large. Its point of origin was above the thrombus. There was a large infarct involving the lower half of the anterior surface of the left ventricle, the apex and the lower 3 cm. of the posterior surface of the left ventricle. The entire apex of the heart was necrotic. The interventricular septum was almost completely infarcted and was in a state of liquefaction necrosis. A large mural thrombus was found in the left ventricle. The base of the right lung disclosed a recent infarct.

The electrocardiograms are shown in figure 1. The first, taken on December 13, showed left bundle branch block. There were deviations of the RS-T interval in leads IV and V. However, in the presence of the bundle branch block we did not know whether or not these deviations of the RS-T interval signified acute cardiac infarction. By December 15 the bundle branch block had disappeared, and lead IV showed the typical signs of a recent infarct in the anterior wall.[2] The deviation of the RS-T interval in lead V was somewhat less than that in lead IV. Lead VI showed a slight elevation of this interval. The limb leads showed a small elevation of the RS-T interval in all leads, most marked in lead II. The third tracing, taken on December 18, showed some diminution in the deviations of the RS-T interval. The last tracing, taken on December 2, showed a return of the limb leads to normal. The chest leads still showed evidence of the acute myocardial lesion.

Summary.—The case was one of coronary occlusion showing electrocardiographic signs of acute anterior infarction and certain indications that the lesion extended to the posterior surface of the heart (table 2)

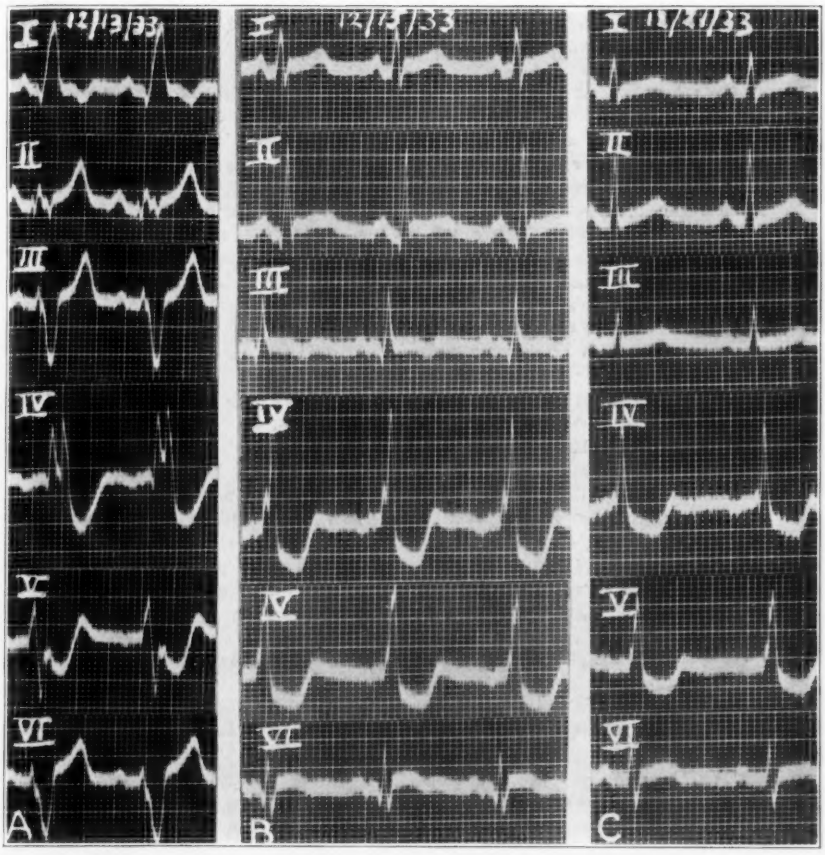

Fig. 1 (case 1).—There was an attack of coronary occlusion on December 11. The leads are numbered I to VI as in a previous publication.[2] The electrode from the anterior wall of the chest was placed over the apex impulse. *A* is the tracing taken on December 13, showing left bundle branch block. The RS-T interval is depressed in leads IV and V. *B* is the tracing taken on December 15. The bundle branch block has disappeared. Lead I shows a slight elevation of the RS-T interval. In lead II the elevation is more marked. In lead III it is very small. Lead IV shows an absence of the initial downward deflection of the QRS complex. The RS-T interval is depressed. Lead V is similar except that the RS-T interval is less deeply depressed. Lead VI shows a slight elevation of the RS-T interval. *C* is the tracing taken on December 21. Leads I, II and III are practically normal. Leads IV and V still show evidence of acute anterior infarction. Leads IV and V, taken with the electrode for the anterior wall on the third interspace on the left near the sternum (not reproduced here), show a much more marked deviation of the RS-T interval. Necropsy, on December 26, showed acute anteroposterior and septal infarction.

and to the interventricular septum (bundle branch block). Necropsy confirmed the electrocardiographic localization.

CASE 2.—H. F. was a bricklayer aged 59. Prior to the present illness he was known to have had elevated blood pressure. He had not suffered anginal pain. On Sept. 19, 1933, he experienced an attack of substernal oppression which was partly relieved by soda. For the next nine days he felt "out of sorts" and had occasional mild pains in the chest. On October 28 he suffered a severe, prolonged attack of substernal pain, vomited, collapsed and thought he was going to die. He was admitted to the Mount Sinai Hospital on October 30 in the service of Dr. Rubenstone. Pain was still present. Cyanosis was noted. The blood pressure was 100 systolic and 65 diastolic. The temperature was 99 F.; the pulse rate was 60, and the respiratory rate was 30. The heart was described as "enlarged to the left." A soft systolic murmur was heard at the apex. The heart sounds were muffled. A tentative diagnosis of acute coronary occlusion was made.

The temperature remained elevated until November 14. Leukocytosis (from 10,400 to 13,400 cells) appeared. The blood pressure remained about 100 systolic and 60 diastolic. Two other attacks of pain occurred, on November 6 and on December 26. The latter was accompanied by elevation of the temperature. The value for blood sugar was elevated (from 150 to 300 mg. per hundred cubic centimeters) throughout the patient's stay in the hospital. The urine showed a small amount of sugar from time to time. Insulin was administered once.

On Jan. 12, 1934, signs of a pleural effusion on the left side were noted. On January 19, 800 cc. of yellowish fluid was removed from the pleural cavity on the left side. The fluid reaccumulated, and tapping was necessary on five occasions. The patient gradually went downhill. The pulse rose to 100. The blood pressure dropped to 90 systolic and 60 diastolic. Pallor, cyanosis and cough were noted. On February 16 a fluoroscopic study of the function of swallowing revealed "slight obstruction to the passage of barium in the lower end of the esophagus. The capsule also passed with difficulty. We believe this partial obstruction to be due to the pressure of an extremely enlarged heart." The patient died suddenly on March 6.

Necropsy was performed on March 7. The right coronary artery was completely occluded on the posterior surface of the heart 5 cm. from its origin. The left anterior descending artery showed marked sclerosis. The lumen of this vessel was considerably narrowed at several points. The circumflex branch of the left coronary artery was completely occluded 5 cm. from its origin and was converted into a solid cord beyond this point. A large aneurysm protruded from the posterior surface of the left ventricle which measured 8 cm. in diameter and 8 cm. in depth. Many thrombi were found in the aneurysm. There was marked sclerosis of the lower third of the anterior surface of the left ventricle. The scarring of this region was continuous with the lesion on the posterior surface.

Electrocardiograms were taken on Oct. 31, Nov. 1, 7 and 14 and Dec. 4, 6, 11, 14, 18, 21 and 26, 1933, and on Jan. 10 and 24 and Feb. 23, 1934. Two of these tracings are shown in figure *2 A*. The first, taken on October 31, showed elevation of the RS-T interval in all three limb leads, most marked in lead II. A deep Q wave was present in lead III. Lead IV showed a depression of the RS-T interval. The initial downward deflection of the QRS complex was preserved. Lead V was within normal limits. Lead VI showed an elevation of the RS-T interval. The second tracing (fig. *2 A2*), taken on December 18, showed the signs of healed infarction of the posterior wall.[2]

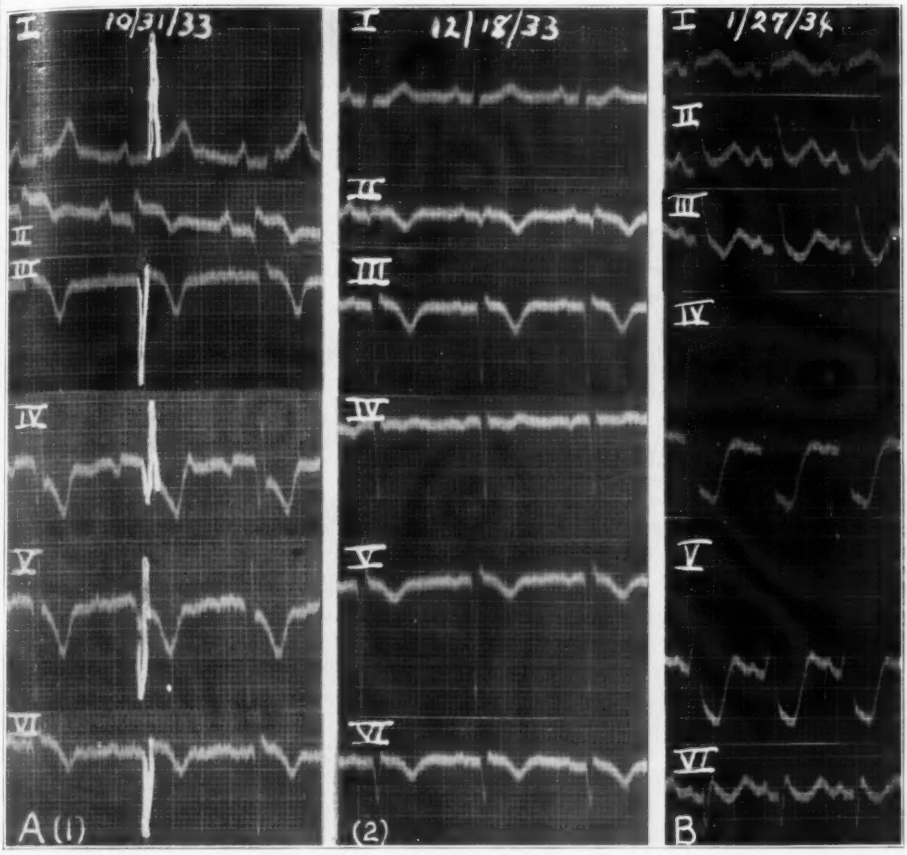

Fig. 2.—*A* shows two tracings made in case 2, in which an attack of coronary occlusion occurred on December 28. The chest leads were taken and numbered as in case 1 (fig. 1). *A1* is the tracing taken on October 31. The RS-T interval is elevated in all three limb leads, most markedly in lead II. There is a deep Q wave in lead III. Lead IV shows a preservation of the initial downward deflection of the QRS complex. The RS-T interval is depressed. Lead V is practically within normal limits. The depression of the RS-T interval is much less marked than in lead IV, and the initial downward deflection of the QRS complex is well preserved. Lead VI shows an upward deviation of the RS-T interval. *A2* is the tracing taken on December 18. It shows evidence of healed posterior infarction,[2] except that the T wave in lead IV is diphasic, not inverted. The signs of the anterior lesion have disappeared. Necropsy on March 7 showed evidence of a previous anteroposterior infarction, the lesion being mainly posterior. *B* shows the tracing for the patient in case 11, taken on January 27. The attack of coronary occlusion occurred on January 22 or before. Lead I shows a slight elevation of the RS-T interval. The RS-T interval in leads II and III is difficult to evaluate. Lead III shows a deep Q wave. Leads IV and V show the typical signs of acute anterior infarction. Lead VI shows a suggestion of elevation of the RS-T interval. Necropsy on January 29 showed acute anteroposterior infarction. The electrocardiographic signs in this case were suggestive but not definite enough to permit the diagnosis of the posteriorly situated part of the acute lesion.

In this case the pathologic evidence was less direct than in case 1 because four months elapsed between the attack and the postmortem examination. However, a lesion involving both the anterior and the posterior surface of the left ventricle was found at necropsy. Therefore it seems probable that on October 31 when the first tracing was taken, both the anterior and the posterior surface of the left ventricle were the seat of acute infarction.

Summary.—The case was one of coronary occlusion which on October 30 showed electrocardiographic evidence of acute infarction in both anterior and posterior surfaces of the left ventricle. The tracings taken subsequently suggested that the main lesion was situated posteriorly. Necropsy four months after the acute attack supported the electrocardiographic localization of the lesion.

Eight other cases have occurred in our series in which the electrocardiographic studies suggested acute infarction of both the anterior and the posterior wall of the left ventricle. Since pathologic confirmation of the location of the lesion was not possible in these 8 cases, they will not be reported in detail. The pertinent data concerning them are summarized in table 1.

The typical phenomena of the RS-T interval produced by the acute anteroposterior lesion are summarized in table 2. Cases 1 to 7 inclusive were illustrative of this group. In cases 8, 9 and 10 a minor variation was evident in that the signs of the anterior lesion did not appear in the limb leads. This was to be expected because a certain number of infarcts of the anterior wall fail to give evidence of their presence in limb leads.[4]

The chief electrocardiographic characteristics of the cases in which both limb and chest leads show evidence of acute anterior and posterior infarction may be summed up as follows:

1. Lead II usually shows a higher deviation of the RS-T interval than leads I or III. This might be expected for the following reasons: *A.* The RS-T interval in lead I tends to be elevated in anterior infarction and slightly depressed or iso-electric in posterior infarction. In anteroposterior infarction these deviations tend to neutralize each other; consequently the RS-T interval in lead I is usually elevated, but less so than in uncomplicated anterior infarction. *B.* The RS-T interval in lead III tends to be elevated in posterior infarction and slightly depressed or iso-electric in anterior infarction. In anteroposterior infarction these deviations tend to neutralize one another. Consequently the RS-T

4. (*a*) Wood, Bellet, McMillan and Wolferth.[2] (*b*) Wood, F. C., and Wolferth, C. C.: Huge T Waves in Precordial Leads in Cardiac Infarction, Am. Heart J. **9**:706 (Aug.) 1934. (*c*) We have seen one other case,[4b] not included in table 1, in which there was evidence of a lesion in the posterior wall in the limb leads. Lead IV showed a huge upright T wave which we believe to be a sign of a lesion in the anterior wall.

TABLE 1.—*Electrocardiographic Evidence Suggesting Acute Infarction of Both Walls of the Left Ventricle in Ten Cases*

Case and Date of Attack	Deviation of RS-T Interval, Mm.						Q Wave in Lead III	Initial Downward Deflection in Leads IV and V	Electrocardiographic Localization	Necropsy	Comment
	I	II	III	IV	V	VI					
1. J. L. 12/12/33	+1	+2	+0.5	−6	−4	+1.5	Very small	Absent	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior; bundle branch block suggested septal lesion	Confirmed electrocardiographic localization	Died 12/26/33 (case 1, fig. 1)
2. H. F. 10/28/33	+1	+2	+1	−3	−1	+1.5	Significant type	Small at first in lead IV; later became normal	Both chest and limb leads showed anterior and posterior lesion; main lesion posterior	Confirmed electrocardiographic localization	Died 3/6/34 (case 2, fig. 2A)
3. S. C. 11/26/33	+1	+2.5	+1.5	−6	−4	+2	Significant type	Absent	Both chest and limb leads showed anterior and posterior lesion; both anterior and posterior lesion equally suggested	0	Died 12/12/33
4. D. F. 3/15/32	+0.5	+1.5	+1	−4	−3	+1	Questionable	Absent	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior	0	Recovered; last heard from on 3/20/34*
5. A. D. 2/6/34	+1	+3	+2	−5	−3	+2	Absent	Absent	Both chest and limb leads showed anterior and posterior lesion; main lesion anterior	0	Recovered; last seen on 7/13/34; condition fair; (fig. 3)
6. H. S. 1/19/33	+2	+3	+1	−4	−1	+2.5	Small	Present	Both chest and limb leads showed anterior and posterior lesion; on 1/20 signs were purely posterior; on 1/23 signs of both; after healing, signs of old posterior lesion alone remained; main lesion probably posterior	0	Discharged 3/24/33; last seen 4/2/34; moderate restriction of activity due to angina on effort
7. M. F. 7/27/33	+0.5	+2	+1.5	−2	0	+2	Significant type	Absent (returned later)	Both chest and limb leads showed anterior and posterior lesion; main lesion probably posterior	0	Died 9/24/33; had several previous attacks suggesting coronary occlusion
8. A. S. 12/7/33	0	+2	+2	−3	0	+2.5	Absent	Small throughout	Limb leads showed posterior lesion only; chest leads showed both anterior and posterior lesion; main lesion probably posterior	0	3/14/33 incomplete heart block developed; died 5/4/34
9. A. S. 2/23/34	−2.5	+2	+4	−4	−1	+3	Significant type	Absent	Limb leads showed posterior lesion only; chest leads showed both anterior and posterior lesion; both anterior and posterior lesion equally suggested	0	Previous attacks 11/8/33 and 2/1/34; died of cardiac failure 5/2/34
10. G. H. 1/27/34	0	+1.5	+1.5	−1	0	+1	Significant type	Absent	Limb leads showed posterior lesion only; chest leads suggested presence of both	0	Previous attack 1/7/34; 3/10/34 in fairly good condition
		T-1 = −4. T-4 = +7 on 2/8/34									

* Wood, Bellet, McMillan and Wolferth,[2] case 18, chart 6.

interval in lead III is usually elevated, but less so than in uncomplicated posterior infarction. *C*. The elevation of the RS-T interval in lead II, the algebraic sum of the elevations in leads I and III, is greater than it is in either lead I or lead III. This is a finding which we have not observed in uncomplicated anterior or posterior infarction. 2. Lead V usually shows less deviation of the RS-T interval than lead IV. Anterior infarction causes a depression of the RS-T interval in lead IV. Posterior infarction usually causes an elevation of the RS-T interval in lead VI. Therefore, the RS-T interval in lead V, the algebraic sum of the elevations in leads IV and VI, shows less deviation than in lead IV. These phenomena of the RS-T interval we believe are the most reliable signs of acute anteroposterior infarction.

TABLE 2.—*Deviations of the RS-T Interval in Acute Cardiac Infarction*

	Anterior	Posterior	Anteroposterior
Lead I	Upward (tend to be largest of the limb leads)	Downward	Tend to be slightly upward
Lead II	Usually none (always less than in lead I)	Upward (always less than in lead III)	Upward (larger than in lead I or lead III)
Lead III	Downward, if any	Upward (tend to be largest of the limb leads)	Tend to be slightly upward
Lead IV	Downward	Often none (upward, if any)	Downward
Lead V	Downward (about equal to those in lead IV)	Upward (tend to be larger than those in lead IV)	Usually downward, but less than in lead IV
Lead VI	Usually none, or slightly downward	Upward	Tend to be slightly upward

The changes in the QRS complex are sometimes helpful. The disappearance of the initial downward deflection in lead IV indicates an anterior lesion; the development of a deep Q wave in lead III following an attack usually indicates a lesion in the posterior wall. When both these signs are present the probability of lesions in both surfaces must be considered (case 11). However, in the absence of the characteristic deviations of the RS-T interval, one cannot tell whether the lesions which produced the changes in the QRS complex are acute or old since these changes tend to persist after healing.

The presence of the typical electrocardiographic signs of acute anteroposterior infarction, outlined in table 2, is probably fairly reliable evidence of the existence of this lesion. On the other hand, the absence of these signs cannot be regarded as certain evidence that such a lesion does not exist. For example, in case 1 the signs of the acute anteroposterior lesion which were present on December 15 were absent on December 21. Only the signs of an anterior lesion remained. In case 11 an electrocardiogram (fig. 2*B*) taken five days (or more) after the

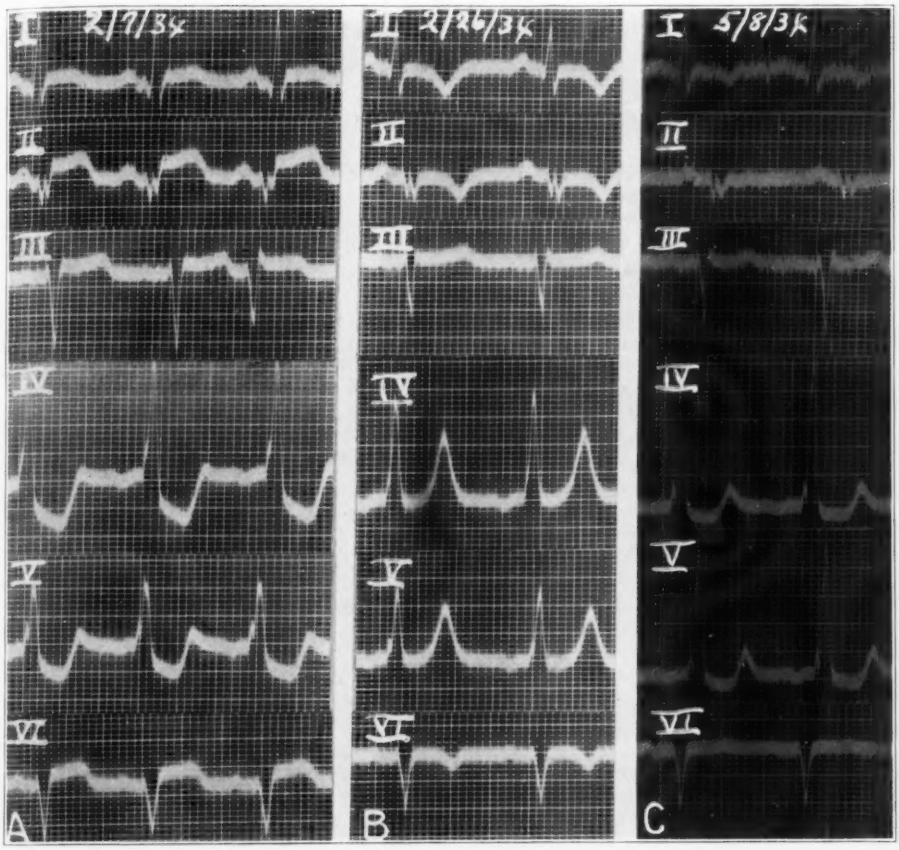

Fig. 3 (case 5).—An attack of coronary occlusion occurred on February 5. The chest leads were taken and numbered as in case 1 (fig. 1). *A* is the tracing taken on February 7. Leads I, II and III show elevations of the RS-T interval. Lead II shows a much more marked elevation than either lead I or lead III. Lead II shows a "W" wave (Edeiken, J., and Wolferth, C. C.: The Clinical Significance of the M and W Shaped QRS Complex in Lead II of the Electrocardiogram, Am. J. M. Sc., to be published). Leads IV and V show the signs of acute anterior infarction, but lead V shows a smaller depression of the RS-T interval. Lead VI shows an upward deviation of the RS-T interval. *B* is the tracing taken on February 26. Leads I and II show a deeply inverted T wave. Lead IV shows a T wave 12 mm. in height. *C* is a tracing taken on May 8. The signs of healed anterior infarction [2] are evident.

onset clearly showed the lesion in the anterior wall, but the signs of the lesion in the posterior wall were doubtful. As healing takes place the major lesion tends to dominate the electrocardiographic picture. The signs of the minor lesion may disappear after a few days.

Case 11 was one of acute anteroposterior infarction proved by necropsy in which the electrocardiographic findings were suggestive but not conclusive.

CASE 11.—F. N. was a Negro woman of 43 with diabetes mellitus. She was admitted on Jan. 26, 1934, to the Philadelphia General Hospital in the service of Dr. Dillon, in diabetic coma. Her husband stated that she had complained of pain in the lower sternal region for about a week prior to admission to the hospital. On January 22 the pain became so severe that she was forced to go to bed. Dyspnea and weakness increased. On the day of admission to the hospital she grew comatose.

Physical examination revealed Kussmaul's breathing, coma and an odor of acetone on the breath. The temperature was 102 F.; the pulse rate was 120, and the respiratory rate was 30. The blood pressure was 90 systolic and 60 diastolic. A loud systolic murmur was heard at the apex. No other abnormalities were noted. The value for blood sugar was 592 mg. per hundred cubic centimeters. The carbon dioxide content of the blood was 19 mg. The leukocyte count was 24,000. The diabetic coma responded satisfactorily to treatment. The acidosis was controlled. Death occurred suddenly on January 28 at 8:55 p. m.

Necropsy was performed by Dr. McCutcheon on January 29. The left anterior descending artery was occluded by a recent thrombus 1 cm. from its origin. The circumflex branch was sclerosed but patent. The lumen of the right coronary artery was narrowed at several points, but never completely occluded. There was an acute infarct involving the lower half of the anterior surface of the left ventricle, the lower half of the ventricular septum and the lower quarter of the posterior surface of the left ventricle. Mural thrombi were adherent to the inner surface of the infarcted area. The ventricular wall near the apex was extremely thin. The ventricular septum bulged toward the right ventricle.

Only one electrocardiographic tracing was taken, on January 27 (fig. 2*B*). Lead I showed a slight elevation of the RS-T interval. In leads II and III it was difficult to be sure where the RS-T interval began, but there seemed to be a slightly high take off in lead II. Leads IV and V showed the typical signs of an acute anterior infarct. Lead VI showed a slightly high take off of the RS-T interval. A deep Q wave was seen in leads III and VI.

Summary.—A case was reported of coronary occlusion with involvement of both anterior and posterior surfaces of the left ventricle. Electrocardiographic evidences of acute infarction of the anterior wall were present. The deep Q wave in lead III and the slightly high take off in leads II and VI suggested the possibility of a lesion of the posterior wall as well.

COMMENT

The only data we possess which serve to indicate the incidence of acute anteroposterior infarction are supplied by the following figures: In 10 of our series of 104 cases of acute coronary occlusion adequately

studied with chest and limb leads, the electrocardiograms showed the signs of this lesion. In 2 of the 20 cases which came to necropsy, we observed this lesion (cases 1 and 11). One showed evidence suggesting a previous acute anteroposterior lesion (case 2).

The cause of the extension of an acute infarct from the anterior to the posterior surface of the left ventricle, or vice versa, would seem to be an anatomic or pathologic variation in the coronary arteries. Consequently one might expect that a patient who had had an infarct in one surface of the heart and who subsequently had a similar lesion in the other would usually show signs of the acute anteroposterior lesion with the second attack. However, this is not necessarily the case. None of the 3 patients in this group who came to necropsy showed a previous infarction of the side opposite the main lesion. Moreover, in 4 other cases of acute cardiac infarction there was no electrocardiographic evidence of an acute anteroposterior lesion, although necropsy in each case showed an acute infarct of one wall of the left ventricle and a healed lesion of the opposite side.

Six of the 10 patients whose cases are reviewed in table 1 have died. Prognostic figures expressed in percentage have little significance in such a small group of cases. However, it would seem that the prognosis of this type of lesion is probably not much more unfavorable than that of the typical infarct of the anterior wall.[1]

SUMMARY

A group of 10 cases is reported in which the electrocardiographic evidence pointed to recent infarction of both the anterior and the posterior wall of the left ventricle. Permission for necropsy was obtained in 2 of the cases. In each instance an infarct was found involving the lower part of the anterior wall, the apex and the lower part of the posterior wall.

The electrocardiographic findings were as characteristic as those of recent infarction limited to the anterior or the posterior wall.

The recognition of the signs of acute involvement of both the anterior and the posterior wall removes a source of confusion in the electrocardiographic localization of myocardial infarction.

Dr. A. I. Rubenstone and Dr. E. S. Dillon gave us permission to report the cases of patients who were under their care.

ACTION OF OIL OF PEPPERMINT ON THE SECRETION AND MOTILITY OF THE STOMACH IN MAN

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AND
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While conducting experiments on the mechanism of pain in peptic ulcer it occurred to one of us to try the effect of essential oils. Oil of peppermint was selected because it is known as a household remedy for relieving gastric distress. This paper is a report of the action of oil of peppermint on the motility and secretion of the stomach of patients with peptic ulcer.

The "Pentsao Kang Mu" (Li Shih Chen, 1597 A. D.),[1] in which is summarized the oldest knowledge of Chinese medicine, records the use of oil of peppermint as an antispasmodic. According to Heupke,[2] peppermint as a remedy was mentioned at the time of Charlemagne.

Wallace and Jackson[3] found that oil of peppermint in the intestine influences gastric secretion by reflex action. Meyer and Gottlieb in their textbook[4] stated that carminatives increase the muscular activity of the alimentary canal. Muirhead and Gerald[5] found that a small amount of a volatile oil increases the motility of isolated segments of intestine and that a larger dose decreases it. Cushny[6] stated that volatile oils relax the musculature of the stomach and intestine. Gunn[7] likewise reported that carminative volatile oils depress

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1. Stuart, G. A.: Chinese Materia Medica, Shanghai, China, American Presbyterian Press, 1911.

2. Heupke, W., and Hollaender, E.: Deutsches Arch. f. klin. Med. **173**:241, 1932.

3. Wallace, G. B., and Jackson, H. C.: Am. J. Physiol. **8**:xvii, 1903.

4. Meyer, H. H., and Gottlieb, R.: Pharmacology, translated by J. Taylor Halsey, Philadelphia, J. B. Lippincott Company, 1915, p. 211.

5. Muirhead, A. L., and Gerald, F. G.: J. Pharmacol. & Exper. Therap. **8**: 253, 1916.

6. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 63.

7. Gunn, J. W. C.: J. Pharmacol. & Exper. Therap. **16**:39, 1920.

the motility of isolated segments of the stomach and intestines. Plant,[8] using dogs with gastric and intestinal fistulas, reported that spirit of spearmint brought into the intestinal loop increases its tone and contractions. Later, Plant and Miller[9] published reports of experiments on segments and strips of intestine in vitro. Small doses of peppermint increase their motility and tone; larger amounts inhibit it. Stross[10] reported that menthol inhibits motility and depresses and abolishes the tonus of isolated pieces of intestine. Arnold[11] noted a paralyzing action of peppermint on the stomach and a stimulating action on the intestine. Sommerfield, Kuenzel and Todd[12] observed with the fluoroscope that peppermint increases the amplitude and vigor of the contractions of the stomach. Heupke and Hollaender,[2] who made an extensive study of the gastric secretory response to many spices and volatile carminative oils, reported that oil of peppermint has no influence on the secretion of hydrochloric acid by the stomach. This is the only paper we have been able to find in the literature which deals with the direct influence of oil of peppermint on gastric secretion. These authors assumed that the beneficial effect of oil of peppermint in epigastric distress is produced by anesthesia of the mucosa of the stomach. One more paper must be mentioned, although it deals with the effect of oil of peppermint on the secretion of bile. Heinz[13] stated that oil of peppermint has a marked cholagogue effect in frogs, rabbits and cats. He also reported good clinical results of its use in man because of this cholagogue action.

We have made the observation on ourselves that the chewing of peppermint candy or lozenges relieves pain caused by hunger and distress after a heavy meal. Tea made from the dried leaves of peppermint is often used by the peasants in France and Germany to relieve abdominal cramps. Much is written in textbooks of pharmacology about an anesthetizing action of oil of peppermint and of menthol on the mucous membranes.

TESTS AND OBSERVATIONS

Effect of Oil of Peppermint on the Secretions of the Stomach During Fasting.—Eleven tests were carried out on nine patients in the fasting state. A Rehfuss tube was introduced into the stomach, and ten minute samples were aspirated. From two to five control samples were taken, and then from 1 to 2 cc. of oil of peppermint (the U. S. P. preparation was used throughout) with 10 cc. of a

8. Plant, O. H.: J. Pharmacol. & Exper. Therap. **16**:311, 1921.

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10. Stross: Arch. f. exper. Path. u. Pharmakol. **95**:5, 1922.

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0.9 per cent saline solution was washed into the stomach through the tube. While in some tests there was a small change in acidity after the oil of peppermint was given, in the majority a considerable reduction of free acid occurred, which is represented in chart 1 by the mean curve. In table 1 the results shown in chart 1 are expressed as percentage of change. The average of the control values is compared with the lowest points of the curves after the oil of peppermint was given. The average decrease thus was 65 per cent. Control tests with 10 cc. of 0.9 per cent saline solution only showed no influence on the free acidity.

Although these results appear to prove a strong depressing action of oil of peppermint on the secretion of free acid by the stomach, more conclusive proof was demanded. The variations of acidity in the stomach of a normal person and of a patient with peptic ulcer may be considerable, and although it is improbable that the variations should work one way only, we wanted better proof. A sufficiently strong secretagogue stimulus was applied to the stomach, first alone, and then with oil of peppermint. Injection of 100 cc. of a 7 per cent solution of ethyl alcohol through the stomach tube and the subcutaneous injection of 0.35 mg. of

TABLE 1.—*Action of Oil of Peppermint (from 1 to 2 cc.) on the Free Acidity of the Stomach After Fasting*

	Free Acid in Clinical Degrees		
Patient	Before	After	± Percentage of Change
1	118	80	−25
2	80	80	0
3	76	50	−33
4	39	0	−100
	60	15	−75
5	45	25	−44
	40	25	−38
6	68	0	−100
7	38	0	−100
8	29	0	−100
9	16	0	−100
Average decrease of acidity			−65

histamine acid phosphate were used.[14] The tests with the secretagogue alone and with oil of peppermint were carried out, of course, on two different days, but in all except two patients they were made within the same week. The areas of both curves for the first two hours after the application of the stimulus were measured with a planimeter and the difference between them expressed as percentage of change.

Eighteen tests were performed on seventeen patients with peptic ulcer. Chart 2 represents the results in a typical case in which complete suppression of free acidity resulted in a patient with peptic ulcer of the duodenum. Alcohol alone produces a good response of free acid, and the same is true for alcohol plus olive oil, while the administration of alcohol plus oil of peppermint is not followed by the secretion of free acid. The combined acid does not show an increase which might explain the disappearance of the free acid; this was true for most of the other tests. The volume of secretion was not changed markedly in this test, although in other tests it was increased. We are aware that comparison of the two areas of secretion involves a great difficulty. The same person has rarely the same degree of free acidity in his stomach at rest. Since the tests were performed

14. Seidmon, E. E., and Necheles, H.: Illinois M. J. **67**:458, 1935.

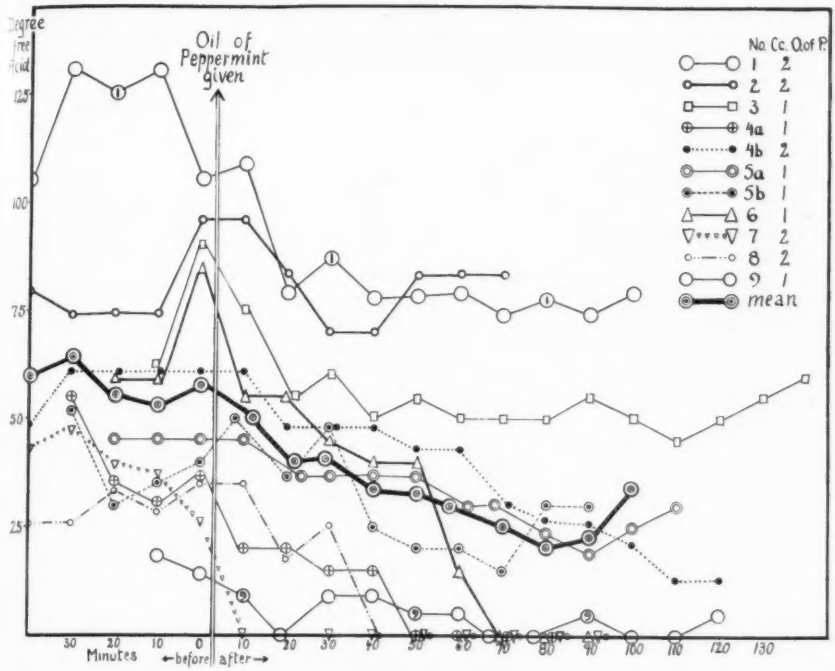

Fig. 1.—The action of oil of peppermint on the gastric secretion of the stomachs of patients with peptic ulcer after fasting.

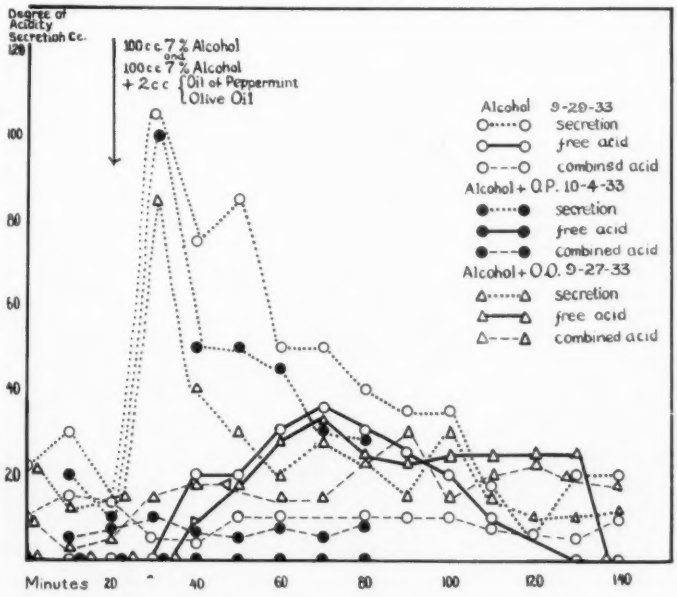

Fig. 2.—Typical results in one patient of a series of tests with alcohol, alcohol and oil of peppermint and alcohol and olive oil.

on two different days, the secretory impulses of the stomach at rest may have been different on the two days, and the action of the oil of peppermint might have been stronger on the day on which the control test was carried out than on the day when the test with oil of peppermint was carried out and vice versa. We therefore have noted the degree of free acid of the stomach after fasting in table 2, both before the alcohol, and before the alcohol and oil of peppermint, were administered.

TABLE 2.—*Results of Tests with Alcohol and with Alcohol and Oil of Peppermint on Patients with Peptic Ulcer* *

No.	Degree of Free Acid in Stomach after Fasting		Percentage of Change in Area after Oil of Peppermint	
	Alcohol	Alcohol-Oil of Peppermint	Free Acid	Secretion
1	98	125	— 46	— 5
2	18	50	— 43	+ 69
3	71	83	— 0.3	+ 2
4	83	111	— 10	+ 32
5	35	23	— 60	— 68
6	10	39	+ 19	+ 84
7	49	23	— 51	— 28
8	63	88	— 43	+113
9	131	25	— 46	+110
10	15	7	—100	+212
11	0	3	—100	— 19
12	33	5	— 71	+ 11
13	35	0	— 56	— 26
14	41	51	— 4	— 9
15	0	5	— 47	— 47
16	0	18	+ 25	— 47
17	30	33	— 43	— 25
	30	35	— 43	+ 17

* The control trials and tests were made within one week except in cases 8 and 10 in which there was an interval of six and eight weeks, respectively.

TABLE 3.—*Comparison of the Free Acidity Before Administration of Alcohol and that Before Administration of Alcohol and Oil of Peppermint*

	Free Acidity Higher in Alcohol Controls	Free Acidity Higher in Alcohol and Oil of Peppermint Controls	Free Acidity the Same in Alcohol and in Alcohol and Oil of Peppermint Controls
Number of times	5	7	6
Percentage of change of area of free acidity after alcohol and oil of peppermint	—57	—13	—56
Percentage of change of area of secretion after alcohol and oil of peppermint	— 1	+35	+22

The depressing effect of oil of peppermint on gastric free acidity was of greater or less significance as the levels for acid after fasting were higher or lower before the administration of alcohol and oil of peppermint than before the administration of alcohol in the control tests.

In table 3 we have grouped the results noted in table 2 accordingly. The most important result was that noted for the group in which the free acidity of the controls of the tests with alcohol and those with alcohol and oil of peppermint were the same, the average decrease in free acidity after the administration of alcohol and oil of peppermint being 56 per cent. In the tests in which the levels of acid after fasting following the alcohol tests were higher, the average decrease

of free acidity was 57 per cent. In those tests in which the acidity of the controls before alcohol and oil of peppermint were given was higher there was a decrease of free acidity of only 13 per cent after alcohol and oil of peppermint were given. These results indicate that there is a clearcut diminution of secretion of acid after alcohol and oil of peppermint are given. There was some increase in the volume of secretion after the administration of alcohol and oil of peppermint.

Histamine is a more powerful gastric secretagogue than alcohol. Simultaneously with the subcutaneous injection of 0.35 mg. of histamine acid phosphate, 2 cc. of oil of peppermint was given through the Rehfuss tube. Except in case 2, in

TABLE 4.—*Results of Tests with Histamine and Histamine and Oil of Peppermint on Patients with Peptic Ulcer*

No.	Degree of Free Acid in the Stomach after Fasting		Percentage of Change in Area after Oil of Peppermint		Interval Between Tests with Histamine and Histamine-Oil of Peppermint, Weeks
	With Histamine	With Histamine and Oil of Peppermint	Free Acid	Secretion	
1	103	61	—51	+ 14	1
2†	25	46	+78	+100	2½
3	14	29	—46	— 20	2½
4	65	54	—24	+ 64	1
5	80	64	—23	— 36	8

* Histamine acid phosphate was given subcutaneously in doses of 0.35 mg. (except in case 3 in which 0.5 mg. was given) and 2 cc. of oil of peppermint was given with 10 cc. of physiologic solution of sodium chloride.

† This patient had hyperthyroid disturbance.

TABLE 5.—*Results of Tests with Alcohol and Alcohol and Olive Oil on Patients with Peptic Ulcer*

Case	Percentage of Change in Area of Secretion of Free Acid	
	After Alcohol and Olive Oil	After Alcohol and Oil of Peppermint
1	—16	—100
2	+27	— 71
3	—17	— 56
4	+16	+ 4
5	+95	+ 25
6	—14	— 43
Average	+16	— 40

which a hyperthyroid condition existed, there was a diminution of secretion of acid in all tests after oil of peppermint was given, even if higher acid levels are accounted for in the controls for the histamine tests (table 4). Since we consider histamine to be so much more powerful a secretagogue than 7 per cent alcohol we expected to find a smaller reduction after alcohol and oil of peppermint than after histamine and oil of peppermint were administered.

In trying to analyze the depressant action of oil of peppermint we made some control experiments on patients on whom tests with alcohol and oil of peppermint had been carried out previously. Olive oil was used in amounts of 2 cc. to exclude the possibility of inhibition of the secretion of acid by oil. In table 5 it is demonstrated that there was no diminution of free acidity similar to that observed after alcohol and oil of peppermint were given. All tests were done within ten days after the control tests were carried out.

Further tests were made in order to find out whether the oil of peppermint would depress the secretion of gastric acid when given thirty minutes after the alcohol or histamine was administered. Four such tests were carried out, and no significant depressing action was demonstrated. Negative results were obtained when menthol (0.5 Gm. in 100 cc. of 7 per cent alcohol), one of the main constituents of oil of peppermint, was given two patients. Phenol (0.1 Gm. in 100 cc. of 7 per cent alcohol) was given once and had a depressant action only slightly lower than that of oil of peppermint.

In one patient in whom there was a good acid secretory response to 100 cc. of 7 per cent alcohol and a complete suppression of free acid after 100 cc. of 7 per cent alcohol plus 2 cc. of oil of peppermint the secretion of mucus was measured. It was thought that increased secretion of gastric mucus after oil of peppermint was given might be responsible for the decrease of the free acidity. The visible mucus was measured by centrifugating every ten minute sample of stomach juice in graduate tubes. Instead of aspirating every sample at the end of each ten minute period continuous suction was used.[15]

As shown in chart 3, there was no increase of secretion of mucus after alcohol and oil of peppermint were given. (The control values for the secretion of mucus

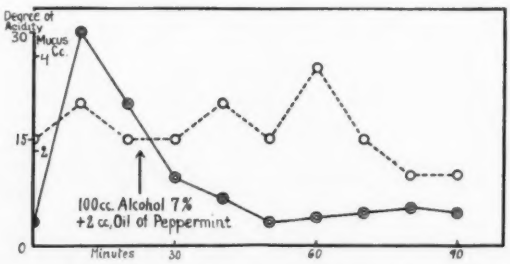

Fig. 3.—The secretion of gastric mucus (unbroken line) and combined acid (broken line) after the administration of 100 cc. of 7 per cent alcohol and 2 cc. of oil of peppermint.

of the resting stomach are always relatively high.) Thus, oil of peppermint does not increase the secretion of visible mucus which might neutralize the free acid and raise the values of the combined acid. No determinations of dissolved mucus were made.

Gastric Motility After Oil of Peppermint Was Given.—Since oil of peppermint might hasten the emptying time of the stomach, patients and dogs were used to investigate this question. The usual balloon method of Carlson and Luckhardt [16] was employed. Through a stomach tube in the patients and through a gastric fistula in the dogs, oil of peppermint was passed after a sufficient period of control. The oil of peppermint was given by constant slow drip or in amounts of from 2 to 4 cc. over a period of time. The experiments lasted from two to six hours.

15. Necheles, H., and Coyne, A.: Secretion of Mucus and Acid by the Stomach in Healthy Persons and in Persons with Peptic Ulcer, Arch. Int. Med. **55**:395 (March) 1935.

16. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1919.

Each kymographic record was divided into twenty minute periods, and the type and height of the contractions [16] of the stomach were tabulated (table 6). As seen in table 6, there was a depression of motility only when large, unphysiologic amounts of oil of peppermint were given. Only once was there a distinct depression of motility in the dog with a relatively small amount of oil of peppermint. These results are somewhat in contradiction to recent experiments carried on in this laboratory and in the roentgen department of Michael Reese Hospital. Normal persons show a considerable decrease in the emptying time of the stomach after a barium sulphate meal plus 2 cc. of oil of peppermint. These results and those obtained by means of the balloon technic will be discussed in another paper.[17]

Experiments on Dogs.—A great number of tests were performed on dogs with stomach pouches (Pavlov and Heidenhain). It could be demonstrated that the secretory action of small amounts of histamine given subcutaneously could be diminished or suppressed completely when simultaneously with the injection of the histamine the pouch was filled with oil of peppermint for five minutes. Oil of peppermint when put into the main portion of the stomach does not have the same effect on the secretion of the pouch. These results will be reported later.[18]

TABLE 6.—*The Action of Oil of Peppermint on Gastric Motility Tested by Means of a Balloon in the Stomach* *

Doses of Oil of Peppermint	Number of Tests	
	Depression of Motility	No Change of Motility
Above 10 cc. in patients; above 4 cc. in dog.....	6	2
Below 10 cc. in patients; below 4 cc. in dog.....	1	11

* Fifteen tests were carried out on thirteen patients with peptic ulcer and five tests on one dog with a gastrostomy.

COMMENT

Oil of peppermint when given by itself or with a secretory stimulant depresses the secretion of acid by the stomach. The mechanism of the depressing action of oil of peppermint on gastric acidity has not been explained to our satisfaction. The rôle of the chlorides was considered as a possible factor. A number of determinations of the chloride content have been made on samples of gastric juice before and after the introduction of alcohol and of alcohol and oil of peppermint into the stomach. The level of the chlorides was not affected when the free and combined acidity decreased after alcohol and oil of peppermint were given. This may be indicative of a change in the mechanism of secretion, i. e., suppression of the free hydrochloric acid and possible increase of the sodium chloride.

17. Sapoznik, H. I.; Arens, R. A.; Meyer, Jacob, and Necheles, H.: The Effect of Oil of Peppermint on the Emptying Time of the Stomach, J. A. M. A. **104**:1792 (May 18) 1935.

18. Necheles, H., and Meyer, Jacob: Am. J. Physiol. **110**:686, 1935.

Oil of peppermint is a mixture of a number of substances,[19] and further analysis of the action of its components is necessary. One of its most characteristic constituents, menthol, was found to have no acid-depressing effects. The oily constituents certainly are not enough in quantity in 2 cc. amounts of oil of peppermint to exhibit the typical depressant action of oil on gastric secretion, and, besides, this has been found in a number of control tests with olive oil. The experiments on dogs with gastric pouches indicate that the action of the oil is probably a local one on the mucosa of the pouch.

If one accepts the evidence given by Heinz [18] that oil of peppermint increases the secretion of bile, this fact helps to explain the popular belief in the favorable action of oil of peppermint in relieving distress caused by gastric hyperacidity. The acid that is still secreted by the stomach is more readily neutralized by the increased volume of bile meeting it in the duodenum. Of course, one must consider here the time relations, i. e., the question of how soon more bile is emptied into the duodenum after the injection of oil of peppermint and how much faster the stomach actually empties itself.

A number of patients with peptic ulcer are now being treated in our clinic with the essence of oil of peppermint. In a few, relief of pain has definitely been noted but the period of observation is not sufficient to warrant a statement. In view of the popular use of peppermint for relief of gastric distress and the interest and importance of the mechanism of pain in ulcer it might readily be argued by those who favor the theory of acid in relation to pain that the relief of symptoms following the use of oil of peppermint is due to a diminution in free acid. However, there is still considerable dispute as to the factors involved in pain in peptic ulcer.[20] In a previous article one of us proved that relief of pain occurred independent of the degree of free acidity in patients with chronic peptic ulcer. It was suggested that the relief of symptoms in patients with peptic ulcer following the use of foreign protein was due to an improvement of the circulation in the vascular bed in and about the ulcerated area, and the hypothesis was advanced that the pain of ulcer is due to ischemia and asphyxia resulting from depletion of the vascular bed in and about the ulcerated area.[21] It was on the basis of this conception of the mechanism of pain in peptic ulcer that it occurred to one of us to try the effects of an essential oil, a substance which might

19. Kremers, R. E.: J. Biol. Chem. **50**:31, 1922.

20. Hurst, A. F.: The Goulstonian Lectures on the Sensibility of the Alimentary Canal, New York, Oxford University Press, 1911. Carlson, A. J.: Am. J. Physiol. **45**:81, 1917. Ivy, A. C.: Contributions to the Physiology of the Stomach: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

21. Meyer, Jacob, and Kartoon, L. B.: The Effect of Intravenous Injections of Foreign Protein on Peptic Ulcer, Arch. Int. Med. **46**:768 (Nov.) 1930.

cause a local hyperemia. The sense of warmth and feeling of ease following the ingestion of essence of oil of peppermint is well known. While we hope to report further on the mechanism of pain, the present study has been directed to an investigation of gastric secretion and motility following the administration of oil of peppermint.

SUMMARY

In patients suffering from peptic ulcer the secretion of acid of the stomach at rest (basal secretion) is depressed or inhibited by oil of peppermint. While the secretion of acid by the stomach of patients with peptic ulcer was abundant after alcohol and histamine were given in control tests, it was completely abolished in some instances and considerably diminished in most instances after simultaneous administration of oil of peppermint. This depression was probably due not to the neutralizing effect of visible mucus but to a local effect on the mucosa and to a shortening of the emptying time of the stomach.

ACUTE CARBON TETRACHLORIDE POISONING

REPORT OF A CASE

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The dangers of carbon tetrachloride and its popularity in commercial preparations have been stressed recently.[1] Many cases of industrial and accidental poisoning have been reported,[2] but laboratory data on actual cases comparable to those available from experimental studies on animals is still lacking.[3] The case reported here is presented to illustrate the important changes in the plasma lipids observed in a case of severe damage to the liver.

REPORT OF A CASE

History.—An unemployed white man 38 years old, for eight years accustomed to drink about 2 pints (946.3 cc.) of ethyl alcohol once or twice weekly, was admitted to the Boston City Hospital eight hours after drinking 4 or 5 ounces (118 to 148 cc.) of pure carbon tetrachloride mistaken for ethyl alcohol.

There was no untoward reaction for three hours; then vomiting occurred immediately after eating, followed by intermittent periods of mental cloudiness and confusion. A physician who was called gave the patient gastric lavage, administered sodium bicarbonate and solutions of egg white and advised immediate hospitalization.

One hour before admittance the patient had severe colicky abdominal pains with numerous watery stools accompanied by large amounts of flatus and tenesmus.

Physical Examination.—Examination revealed a well developed and well nourished man who was obviously ill. The breath had a definite odor of carbon tetrachloride. The skin was pale, cold and slightly cyanotic. The tongue was coated. The heart was slightly enlarged. The sounds were regular and of fair quality. There were a short systolic murmur at the apex and a soft diastolic murmur heard best over the area of the mitral valve. The second aortic sound was louder than

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From the Laboratory for Surgical Research of the Boston City Hospital.

1. Volatile Poisons in the American Home, editorial, J. A. M. A. **101**:1238 (Oct. 14) 1933.

2. McMahon, H. E., and Weiss, S.: Carbon Tetrachloride Poisoning with Macroscopic Fat in the Pulmonary Artery, Am. J. Path. **5**:623 (Nov.) 1929. Butsch, W. L.: Cirrhosis of the Liver Caused by Carbon Tetrachloride, J. A. M. A. **99**:728 (Aug. 27) 1932. Poisoning from Carbon Tetrachloride, foreign letter (Paris), ibid. **99**:1276 (Oct. 8) 1932. McGuire, L. W.: Carbon Tetrachloride Poisoning, ibid. **99**:988 (Sept. 17) 1932.

3. Lamson, P. A., et al.: The Pharmacology and Toxicology of Carbon Tetrachloride, J. Pharmacol. & Exper. Therap. **22**:215 (Nov.) 1923.

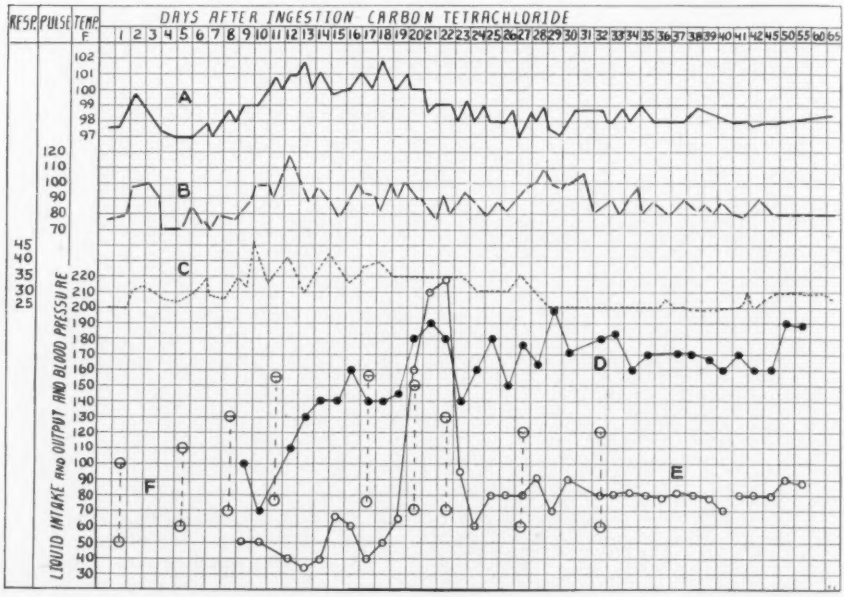
Laboratory Data and Parenteral Medication in a Case of Carbon Tetrachloride Poisoning

Days After Ingestion of Poison	Plasma Lipids, Mg. per 100 Cc.						Chemical Analysis of Blood, Mg. per 100 Cc.						Studies of the Blood			Urinalysis					Parenteral Medication		
	Cholesterol						Nonprotein Nitrogen											Sediment			Intravenous		
	Total	Free	Ester	Total Fatty Acids	Phospholipid	Total Lipid	Icteric Index	Bilirubin, Mg. per 100 Cc.	Total	Urea	Amino Acid	Uric Acid	Creatinine	Sugar	Hemoglobin (Sahli), per Cent	Red Cells*	White Cells*	Specific Gravity	Albumin	Red Cells†	White Cells†	Casts†	Hypodermoclysis,‡ Cc.	50% Dextrose, Cc.	Calcium Gluconate, Gm.
1	..	..	..	...	...	...	..	...	...	...	...	....	...	...	90	5,140	16.8	1.007	SPT	0	2 to 3	0	.....	...	...
2	..	..	..	...	...	...	..	...	...	...	...	....	...	...	94	4,510	11.0	1.021	0	0	0	0	1,250	125	0.8
3	..	..	..	...	...	...	..	...	...	...	...	....	...	...	..	.....	....	1.020	Trace	0	10 to 15	§	.....	...	...
4	..	..	..	...	...	...	..	...	...	...	...	....	...	...	..	.....	5.8	1.021	0	0	0	0	2,400	200	1.0
5	74	45	29	218	86	292	55	3.5	...	...	...	....	...	...	..	.....	4.1	.....	..	..	..	..	2,400	200	1.0
6	78	..	..	277	86	355	45	2.5	135	146	6.3	13.0	7.2	99	91	5,560	9.1	.....	..	..	..	..	2,200	100	1.0
7	86	54	32	338	166	424	50	2.5	132	116	5.9	11.5	7.6	94	..	.....	...	1.010	ST	0	0	0	2,100	190	1.0
8	89	22	67	268	111	357	65	2.3	136	95	7.1	11.0	4.0	112	..	.....	...	1.010	ST	0	0	0	1,000	100	1.0
9	81	36	45	370	168	451	25	2.5	123	95	5.8	10.4	6.1	110	..	.....	...	1.010	SPT	0	0	0	1,500	150	1.3
10	95	17	78	254	118	349	45	2.0	...	...	...	....	...	...	..	.....	...	1.010	VST	0	0	0	1,500	150	1.5
11	86	37	49	271	157	357	18	1.8	119	73	5.1	9.0	4.5	122	..	.....	...	1.010	VST	0	0	0	500	100	0.0
12	80	25	65	345	149	425	20	2.0	122	62	5.7	9.4	4.0	...	65	3,250	13.5	1.009	VST	0	0	0	1,200	100	1.0
13	..	..	..	...	...	...	..	...	...	...	...	....	...	...	..	.....	....	1.012	VST	0	0	0	1,000	100	1.0
14	97	46	51	349	121	446	25	2.5	85	56	4.9	6.4	3.1	120	..	.....	....	1.012	VST	0	0	0	1,000	100	1.0
15	...	..	..	...	...	...	..	...	...	...	...	....	...	...	63	2,900	11.9	1.011	SPT	0	0	0	800	80	0.8
16	105	38	67	318	108	423	20	2.0	77	52	...	5.2	2.1	98	..	.....	....	1.013	VST	0	0	0	000	000	0.0
17	...	..	..	...	...	...	..	...	...	...	...	....	...	...	58	3,100	14.3	1.009	VST	0	0	0	000	50	0.0
18	103	18	85	332	116	435	15	1.5	49	40	6.4	4.8	...	105	..	.....	....	1.012	VST	0	0	0	000	000	0.0
25	106	45	61	365	148	471	5	0.0	28	29	6.0	2.6	...	106	65	2,850	12.0	1.012	0	0	0	0	000	000	0.0
30	118	36	82	377	...	495	7	0.0	31	12	6.3	3.3	1.1	70	..	.....	....	1.013	0	0	0	0	000	000	0.0
41	128	69	59	576	176	704	5	0.0	23	7	5.0	2.4	...	73	70	3,930	8.2	1.014	0	0	0	0	000	000	0.0
62	187	55	129	463	170	674	5	0.0	30	14	6.7	3.8	...	95	82	4,700	8.7	1.008	0	0	0	0	000	000	0.0

* These are given in thousands per cubic millimeter of whole blood.
† These were estimated per high power field.
‡ Physiologic solution of sodium chloride.
§ Many granular casts.

the second pulmonic sound. The arterial blood pressure was 105 millimeters of mercury systolic and 50 mm. diastolic. The lungs were clear. The abdomen was not distended, but there were generalized muscular spasm, resistance and tenderness on palpation. No mass was felt. There was no evidence of ascites. The extremities were normal. All the reflexes were hyperactive.

Treatment and Clinical Course.—A therapeutic regimen intended to combat damage to the liver was instituted. This consisted of a diet high in carbohydrate (200 Gm. daily), daily intravenous injections of dextrose and calcium gluconate (table), oral administration of 1.8 Gm. of calcium lactate daily and rectal administration of a solution of dextrose (120 cc. of a 10 per cent solution every four hours).



A record of the temperature (*A*), pulse rate (*B*), respiratory rate (*C*), fluid intake (ounces), (*D*), fluid output (ounces), (*E*) and systolic and diastolic blood pressure (millimeters of mercury) (*F*) in a case of acute carbon tetrachloride poisoning.

The patient complained of severe abdominal cramps and generalized aches and pains in the muscles, and was unable to retain fluids given by mouth during the first three days. The watery stools passed frequently during the first thirty-six hours had an unmistakable odor of carbon tetrachloride. On the third day the sclerae showed definite evidence of jaundice. On the sixth day the patient became dyspneic and had a dry, hacking cough. The sputum was watery and contained many red cells. On the tenth day there was pitting edema of the ankles, sacrum and scrotum. Shifting dulness was demonstrated in the abdomen at this time. The lungs contained many râles, which were most marked at the bases and in

the midanterior regions. The temperature rose to 102 F. and remained elevated until the twenty-first day (chart).

Roentgenograms of the chest at this time showed bilateral consolidation of the lungs similar to that seen in cases of bronchopneumonia (roentgen studies of the chest are given later). The patient was dangerously ill during the first three weeks.

Eighteen grains (1.17 Gm.) of digitalis was given during the thirteenth and fourteenth days. Administration of digitalis was continued in a daily dose of 1½ grains (0.097 Gm.) through the twenty-sixth day when it was omitted until the fiftieth day. The patient then received 3 grains (0.195 Gm.) daily for seven days.

Improvement was rapid after the twenty-first day. There was temporary diuresis (chart) with the disappearance of the ascites and edema. The patient was symptom-free in five weeks and remained so until his discharge from the hospital on the sixty-fifth day after drinking the poison.

The chart shows the temperature, pulse rate, respiratory rate, fluid intake, urinary output and systolic and diastolic arterial blood pressure. The laboratory data are given in the table.

Roentgen Studies of the Chest.—On the fourteenth day there was a diffuse bilateral mottling similar to that seen in cases of bronchopneumonia or advanced tuberculosis. This picture was interpreted as possibly being due to multiple fat emboli in the lungs. On the sixteenth day there was irregular density throughout both pulmonary fields which was most marked in the upper third and about the hili. The density was interpreted as being due to a consolidation of the parenchyma. On the twenty-sixth day there was less consolidation than was seen in the previous picture. The consolidation was still present in the upper third of the right side, and the picture was consistent with that of bronchopneumonia in the convalescent stage. On the thirty-sixth day the lungs were clear except for a faint cloudiness at the base of the right lung. On the fiftieth day and on the sixty-second day the chest appeared normal.

Electrocardiograms.—On the eleventh day there was evidence of sino-auricular tachycardia with a rate of 103 and a PR interval of 0.14 second. There were high P_2 and P_3 waves. The QRS interval was 0.09 second. The T wave was upright in all leads; the T_3 wave was high. The axis was normal. On the fiftieth day there was normal sinus rhythm, with a rate of 73, a PR interval of 0.16 second and a QRS interval of 0.08 second. The T_1 wave was flat and the T_2 and T_3 waves were inverted. The axis was normal. On the sixty-second day there was evidence of sinus arrhythmia, with a rate of 80, a PR interval of 0.14 second and a QRS interval of 0.09 second. The T_1, T_2 and T_3 waves were upright and the axis was normal.

Studies of the Blood.—Values for each of the plasma lipids was diminished on the fifth day when the plasma was first examined. The allocation of total cholesterol showed a predominance of the free form. This altered ester cholesterol-total cholesterol ratio gradually changed with recovery, and the ratio was normal at the time of the patient's discharge from the hospital. The phospholipid and fatty acid fractions mirrored the gross changes shown by the variations in total lipids and cholesterol. The fatty acid fraction became normal sooner than the cholesterol fraction.

The value for nonprotein nitrogen was normal on the second day, but on the sixth day there was a marked retention of all the nitrogenous substances. The values for urea, uric acid and creatinine were each increased early and gradually returned to normal during convalescence. The amino-acid nitrogen content was

not altered. The value for blood sugar showed no definite correlation with the other laboratory or clinical observations. The high icteric index and bilirubin values showed a tendency to approximate a minimal ratio of 10 to 1 during convalescence.

Polymorphonucleosis was present on admission. The count dropped quickly to normal but rose again with the inception and for the duration of the pathologic process in the lungs. Marked secondary anemia was present at the onset of the edema; it responded slowly to treatment with ferric ammonium citrate (table). A differential count on the second day showed 64 per cent polymorphonuclears, 24 per cent lymphocytes, 8 per cent mononuclears, 2 per cent basophils and 2 per cent eosinophils; a differential count on the forty-first day showed 60 per cent polymorphonuclears, 25 per cent lymphocytes, 10 per cent mononuclears, 2 per cent eosinophils and 3 per cent basophils. The bleeding time was two minutes on the fourth day, four minutes on the tenth day and two and one-half minutes on the thirtieth day. The clotting time was two and one-half minutes on the tenth day and three minutes on the thirtieth day (capillary tube method). The plasma protein and the carbon dioxide capacity were 6.4 per cent and 52.3 per cent, respectively, on the thirtieth day. The Kahn test was negative.

Studies of the Urine.—The urine contained macroscopically visible bile on the second and the third day. The phenolsulphonphthalein test of renal function showed an excretion of less than 10 per cent in two hours on the ninth and the eleventh day. The first of these tests was performed on the day before the edema was noted. The urea clearance test gave supportive evidence of dysfunction of the kidneys. On the sixteenth day excretion of urea was 28 per cent of normal, and on the forty-seventh day, 50 per cent. The temporary urinary retention was in contrast with the small amount of albumin, red cells and casts found in the urine (table).

Examination of the Stools.—The stools for the first thirty-six hours were watery and contained a large amount of carbon tetrachloride, and the benzidine test for blood was positive. After the fourth day the stools were brown and formed.

COMMENT

A typical course following the experimental feeding of carbon tetrachloride to animals consists in vomiting, diarrhea, neurologic disturbances, jaundice and excretion of the poison through the lungs.[4] Recovery from the poison is materially affected by the availability of calcium and dextrose.[5] Postmortem examination of the animals at varying intervals after the ingestion of the poison reveals characteristic changes in the liver and minor changes in the lungs, kidneys and other organs.[6] The microscopic changes in the kidneys are not outside the normal limits, as indicated by observations on control animals.[6]

4. Bollman, J. C., and Mann, F. C.: Experimentally Produced Lesions of the Liver, Ann. Int. Med. **5**:699 (Dec.) 1931. Lamson et al.[3]

5. Minot, A. S., and Cutler, J. T.: Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, J. Clin. Investigation **6**:369 (Dec.) 1928.

6. Gardner, G. H., et al.: Studies on the Pathological Histology of Experimental Carbon Tetrachloride Poisoning, Bull. Johns Hopkins Hosp. **36**:107 (Feb.) 1925.

The course in our case of accidental poisoning followed closely that observed in animals during the acute stage. The prognosis cannot be determined until several years have elapsed in order to exclude the possible development of cirrhosis of the liver or other delayed pathologic changes resulting from the acute poisoning. However, the patient has been symptom-free for one-half year.

The laboratory data corroborate the clinical findings. The low values for the plasma lipids are consistent with the values in cases of jaundice due to damage of the liver.[7] The diminished cholesterol ester-total cholesterol ratio was due largely to a decrease in the form of the ester and was related to the esterifying function of the liver.[8] The increased nonprotein nitrogen content coincident with the diminished function of the kidneys shown by the tests indicate that a temporary upset in the function of the kidney occurred; but it also suggests possible close relations between the liver and the kidneys.[9] The gradual approach of the icteric index and the bilirubin values during convalescence to a minimal ratio of 10 to 1 is consistent with the recovery of the function of the liver and the decreased stasis of bile pigment in the blood stream. Larger discrepancies between these values are found in jaundice associated with stasis of bile pigment in the blood stream or with the regurgitation of pigments other than bilirubin from the biliary system. A large amount of bile pigment in the blood stream interferes with the determination of hemoglobin by the usual colorimetric methods (Tallqvist and acid hematin).[7] The presence of secondary anemia emphasizes the probable widespread effect of the circulating poison on all tissue with which it came in contact.

SUMMARY

A severe case of accidental poisoning with carbon tetrachloride occurring in a man addicted to alcohol is reported with laboratory data which indicated the widespread effect of the drug.

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7. Lehnherr, Earl R.: The Value of Icteric Indices and Plasma Lipids in the Diagnosis of Jaundice, New England J. Med. **211**:487 (Sept. 13) 1934.

8. Thannhauser, S. J.: Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, Munich, J. F. Bergmann, 1929, p. 486.

9. Pick, E. P.: Regulation of Water Metabolism, Harvey Lectures, 1929-1930, Baltimore, Williams & Wilkins Company, 1931, p. 25. Glaubach, S., and Molitor, H.: Die diuresefördernde Wirkung von Leberextrakt bei niereninsuffizienten Hunden, Wien. klin. Wchnschr. **42**:1437 (Nov. 7) 1929. Heyd, Charles G.: "Liver Deaths" in Surgery of the Gallbladder, J. A. M. A. **97**:1847 (Dec. 19) 1931. Schutz, Carl B.; Helwig, Ferdinand C., and Kuhn, Harold P.: A Contribution to the Study of So-Called Liver Death, J. A. M. A. **99**:633 (Aug. 20) 1932.

The values for each of the plasma lipids was low for the probable duration of the damage of the liver as evidenced by the clinical findings. The low values for total cholesterol and the diminished ester cholesterol-total cholesterol ratio are considered typical of jaundice due to damage of the liver.

The low lipid values occurred simultaneously with the retention of nitrogenous substances in the blood stream and may be significant in suggesting a close relationship between the functions of the liver and those of the kidneys.

Progress in Internal Medicine

DISEASES OF THE ADRENAL GLANDS

A REVIEW WITH SPECIAL REFERENCE TO THE CLINICAL ASPECTS

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ROCHESTER, MINN.

In their monograph on Addison's disease, Rowntree and Snell [1] in 1931 summarized the essential features of what was known about the physiology of the adrenal glands as follows:

> Without discounting the value of studies on extirpation of the gland and on the preparation of glandular extracts, it must be said that the exact physiologic functions of the suprarenal gland in the intact animal are uncertain. Our exact knowledge of the physiology of the suprarenal glands can be expressed in two statements: the cortex of the gland is essential to life, and the medulla of the gland, although apparently not a vital organ, secretes a substance which is normally present in the blood stream and which has powerful pharmacodynamic properties. Of the multitude of other functions which have been suggested, few rest on adequate experimental grounds.

They referred the reader wishing to pass critical judgment on much that is written on the physiology of these glands in health and disease to the excellent reviews of Stewart,[2] Jaffe,[3] Goldzieher [4] and Biedl.[5] At that time cortical extracts of the adrenal glands had been prepared by Rogoff and Stewart,[6] by Hartman and his collaborators [7] and by

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Dr. Albert M. Snell and Dr. Robert L. Parker assisted in the preparation of this manuscript.

1. Rowntree, L. G., and Snell, A. M.: A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

2. Stewart, G. N.: (*a*) Adrenalectomy and the Relation of the Adrenal Bodies to Metabolism, Physiol. Rev. **4**:163 (April) 1924; (*b*) Blood Studies in Dogs After Adrenalectomy, J. Pharmacol. & Exper. Therap. **29**:373, 1926.

3. Jaffe, H. L.: The Suprarenal Gland, Arch. Path. **3**:414 (March) 1927.

4. Goldzieher, M. A.: The Adrenals: Their Physiology; Pathology, and Diseases, New York, The Macmillan Company, 1929.

5. Biedl, Arthur: Die geschichtliche Entwicklung der Kentnisse ueber die Nebenniere bis Addison (1855), Janus **15**:294, 1910.

6. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency: IV. The Influence of Intravenous Injections of Ringer's Solution upon the Survival Period in Adrenalectomized Dogs, Am. J. Physiol. **84**:649 (April) 1928; Studies on Adrenal Insufficiency in Dogs: V. The Influence of Adrenal Extracts on

(Footnotes continued on next page)

Swingle and Pfiffner,[8] and a number of patients with Addison's disease had been treated with some success by the administration of Swingle and Pfiffner's extract.[9]

Although Rowntree and Snell's [1] conclusions are in the main true today, some progress has been made, and it is my purpose in this paper to discuss briefly some phases of this progress which appear to be related to diseases of the adrenal glands.

In the following résumé of the newer work it has been necessary for the sake of proper perspective to review not only some of the older literature but also some material which may seem elementary to those primarily interested in endocrinology. Scant attention has been paid to the medullary portion of the gland. This was done deliberately, as very little could be added to what has already been written and ably reviewed many times. This does not imply that in the last five years no work of value has been done on the physiology of the adrenal medulla and its hormone, epinephrine. Many contributions have been made, especially on the relationship of the medulla and epinephrine to carbohydrate metabolism. This phase of the subject was reviewed in 1935 by Wilder and Wilbur.[10] The pharmacologic properties of epinephrine are still a subject for study, and considerable work has been done on the relationship of the medulla to the problem of essential hypertension. Nevertheless, whether rightly or not, the general conception still obtains that the adrenal medulla is a relatively inert organ except in times of emotional stress when it discharges epinephrine. It appears likely that when some of the problems associated with the cortex are clarified more attention will again be directed to the medullary portion of the gland.

Survival Period of Adrenalectomized Dogs, ibid. **84**:660 (April) 1928; Suprarenal Cortical Extracts in Suprarenal Insufficiency (Addison's Disease), J. A. M. A. **92**:1569 (May 11) 1929.

7. (*a*) Hartman, F. A., and Brownell, Katherine A.: The Hormone of the Adrenal Cortex, Science **72**:76 (July 18) 1930. (*b*) Hartman, F. A.; Brownell, Katherine A.; Hartman, W. E.; Dean, C. A., and MacArthur, C. G.: The Hormone of the Adrenal Cortex, Am. J. Physiol. **86**:353 (Sept.) 1928. (*c*) Hartman, F. A.; MacArthur, C. G., and Hartman, W. E.: A Substance Which Prolongs the Life of Adrenalectomized Cats, Proc. Soc. Exper. Biol. & Med. **25**:69 (Oct.) 1927.

8. Swingle, W. W., and Pfiffner, J. J.: (*a*) An Aqueous Extract of the Suprarenal Cortex Which Maintains the Life of Bilaterally Adrenalectomized Cats, Science **71**:321 (March 21) 1930; (*b*) Further Observations on Adrenalectomized Cats Treated with an Aqueous Extract of the Suprarenal Cortex, ibid. **71**:489 (May 9) 1930; (*c*) The Revival of Comatose Adrenalectomized Cats with an Extract of the Suprarenal Cortex, ibid. **72**:75 (July 18) 1930.

9. Rowntree, L. G.; Greene, C. H.; Swingle, W. W., and Pfiffner, J. J.: Addison's Disease: Experiences in Treatment with Various Suprarenal Preparations, J. A. M. A. **96**:231 (Jan. 24) 1931.

10. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **55**:304 (Feb.) 1935.

PHYSIOLOGY

If both adrenal glands are removed from animals a characteristic series of phenomena take place. In dogs, for example, nothing appears to happen for a period which varies from twelve hours to several days. The dogs then become easily fatigued and are apathetic; they refuse to eat and finally become exceedingly weak. The blood pressure, blood volume, basal metabolic rate, consumption of oxygen and body temperature decrease. Invariably the dogs lose weight; as they decline they usually go into a coma or a semistuporous condition, and just before death muscular twitchings and convulsions may appear. Death occurs in from three to eleven days after the operation. Considerable difference of opinion exists regarding the duration of this period of survival. Certain chemical changes take place which parallel the clinical picture. The concentration of the nonprotein nitrogen in the blood increases, largely as the result of an increase in the value for blood urea. The blood loses water and becomes thick and viscid. This loss of water is shown by an increased concentration of proteins in the blood and by an increase in the number of erythrocytes per unit of volume. Low values for blood sugar and symptoms of hypoglycemia are encountered frequently, and a remarkable series of changes in the concentration of various electrolytes takes place both in the blood and in the tissues. These changes will be considered in detail later. Following injection of the cortical hormone the animal improves, and the chemical constituents of the blood may again become normal.

Although practically all workers are agreed regarding the facts just stated, considerable difference of opinion has arisen regarding their interpretation. Four theories regarding the action of the cortical hormone have been propounded. Hartman, Brownell and Lockwood [11] demonstrated that the hormone is directly related to muscular fatigue and that it prevents the diminished resistance to cold and heat encountered in adrenalectomized animals. Because of its relationship to these factors as well as to others, such as metabolism, growth, fluid balance and probably renal function, they arrived at the conclusion that the cortical hormone is closely related to the function of all tissues and suggested that it might be considered as a general tissue hormone. Kendall, commenting on the work of Koelsche [12] (who demonstrated that following the injection of thyroxin the cortical hormone prevents the usual loss of nitrogen in both unilaterally and bilaterally adrenalec-

11. Hartman, F. A.; Brownell, K. A., and Lockwood, J. E.: Studies Indicating the Function of Cortin, Endocrinology **16**:521 (Sept.-Oct.) 1932.

12. Koelsche, G. A.: The Relation of the Suprarenal Cortical Hormone to Nitrogen Metabolism, Proc. Staff Meet., Mayo Clin. **9**:55 (Jan. 24) 1934.

tomized dogs), stated that Koelsche's results tended to support Hartman's point of view.

One of the earliest theories proposed to explain the action of the adrenal cortical hormone was that of Britton and Silvette [13] who postulated that the adrenal cortex prepotently regulates carbohydrate metabolism and is chiefly concerned with the storage and utilization of carbohydrate. In January 1934 they reviewed the controversy which had developed regarding the function of the adrenal cortex and presented additional evidence to support their own contentions. They pointed out that the adrenalectomized rat suffers from a lack of dextrose and glycogen that becomes progressively more severe after adrenalectomy and parallels the development of the symptoms. (This is not in accord with the findings of Swingle, which will be given later, who used dogs as experimental subjects.) Britton and Silvette further showed that the injection of epinephrine scarcely affects the level of blood sugar in animals with adrenal insufficiency even though the animals are in good condition. This was explained as being the result of depleted glycogen stores in the liver. They also found that the synthesis of glycogen which normally takes place following the injection of dextrose and sodium lactate does not occur in any significant degree in the adrenalectomized animal, and they again called attention to the fact that animals dying of adrenal insufficiency have convulsive seizures some time before death, a fact which could not be explained on the basis of decreased blood volume or circulatory failure. They disputed the evidence offered by Swingle that the dilution of blood in adrenalectomized animals does not occur without the administration of the hormone, and they found that the blood volume could readily be restored by the injection of saline solution but with no relief of symptoms. Satisfactory but temporary response was obtained on administration of solution of dextrose. They found, as did Swingle, a reduction in the blood volume of adrenalectomized animals, although to a lesser extent; in some animals there was no change, and in others the blood volume was elevated. A definite shift of the body fluids seemed to take place, the movement of fluids being from the blood toward the liver and muscles. In a more recent article Silvette [14] stressed the shift in the water and chloride balance that occurs in adrenalectomized animals. This shift is manifested by an increased content of water in the liver and muscles and by a decreased concentration of chloride in the tissues. Silvette expressed the opinion that the lack of hormone

13. Britton, S. W., and Silvette, H.: On the Function of the Adrenal Cortex—General, Carbohydrate and Circulatory Theories, Am. J. Physiol **107**:190 (Jan.) 1934.

14. Silvette, Herbert: Chloride, Carbohydrate and Water Metabolism in Adrenal Insufficiency and Other Conditions, Am. J. Physiol. **108**:535 (June) 1934.

indirectly produces some fundamental condition or factor that is responsible for the shift in the water and chloride balance, and this factor seems to be a deficiency in dextrose and glycogen.

Swingle and Pfiffner and their associates[15] were not impressed by the changes that take place in the carbohydrate metabolism of adrenalectomized animals. In a series of articles they expressed the view that the chief and perhaps the only function of the adrenal cortical hormone is the regulation and maintenance of the normal circulating volume of blood. As a result of their experiments they attempted to show that all other factors are secondary and dependent on the loss of ability to maintain the blood volume. They interpreted their results to indicate that in the absence of the hormone in the adrenalectomized dog fluid is continually lost from the circulation, presumably by transudation. As the result of an insufficiency of circulating fluid the blood pressure falls progressively, the blood becomes unduly concentrated and viscid, renal function fails, and circulatory failure ensues. Adrenalectomized animals, according to them, are apparently unable to draw fluid back through the walls of the capillaries into the blood stream.

Swingle and Pfiffner also pointed out the striking similarity between adrenal insufficiency and traumatic shock and they supported their view by demonstrating that adrenalectomized animals show an unusual sensitiveness to hemorrhage. The removal of 40 cc. of blood from the dogs on which they were experimenting, an amount which in a normal dog would cause no effect, produced profound shocklike effects which are explained by the inability of the animal to restore its blood volume. In the normal mechanism of dilution the rôle of the adrenal cortex thus appears to be that of a mobilizer of water and salt, so that the saline solutions of the tissues and interstitial spaces become available for transfer to the blood stream. In the absence of the cortical hormone such transfer does not occur. In their more recent articles,[16] Swingle, Pfiffner and others devoted considerable attention to the part played by sodium chloride in adrenal insufficiency, and they pointed out that the experimental feeding of sodium chloride to adrenalectomized ani-

15. (*a*) Swingle, W. W.; Pfiffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: The Function of the Adrenal Cortical Hormone and the Cause of Death from Adrenal Insufficiency, Science **77**:58 (Jan. 13) 1933. (*b*) Swingle, W. W.; Pfiffner, J. J.; Vars, H. M., and Parkins, W. M.: The Effect of Hemorrhage on the Normal and Adrenalectomized Dog, Am. J. Physiol. **107**:259 (Feb.) 1934; (*c*) The Effect of Fluid Deprivation and Fluid Intake upon the Revival of Dogs from Adrenal Insufficiency, ibid. **108**:144 (April) 1934; (*d*) The Effect of Sodium Chloride Administration upon Adrenalectomized Dogs not Receiving Extract, ibid. **108**:159 (April) 1934.

16. Swingle, W. W.; Vars, H. M., and Parkins, W. M.: A Study of the Blood Volume of Adrenalectomized Dogs, Am. J. Physiol. **109**:488 (Sept.) 1934. Swingle, Pfiffner, Vars and Parkins.[15b]

mals which were not receiving cortical extract somewhat prolonged the interval between the time that injections of extract were stopped and adrenal insufficiency developed. They concluded that sodium chloride could not be regarded as an effective substitute for cortical hormone in the bilaterally adrenalectomized dog since it was necessary to inject cortical extract in order to save the animals when symptoms sooner or later developed. Swingle and Pfiffner then investigated the water balance and fluid exchange in adrenalectomized dogs which were not receiving cortical extract. Their results indicated that the animals first exhibited a negative water balance and lost more fluids than they took in, and then that the normal exchange of fluid between the blood stream and tissues was upset and transudation from tissues to interstitial spaces impaired, since under these circumstances fluid and salt are not freely mobile. They were of the opinion that these factors taken together satisfactorily explained most if not all of the observed phenomena of adrenal insufficiency, but that taken singly neither factor was adequate to serve as an explanation.

Much of the credit for recognition of the very important part played by sodium chloride in adrenal insufficiency is due to Loeb and his collaborators.[17] He made careful chemical studies of 3 patients with Addison's disease and found in all 3 a decrease in the total base which occurred largely at the expense of the sodium content. In all 3 cases the potassium content of the serum was either at a high normal level or definitely increased. Symptoms of adrenal insufficiency and the associated chemical changes disappeared in 1 case after the administration of sodium chloride. Loeb postulated that the syndrome of adrenal insufficiency may be directly concerned with this loss of base. (The work of Loeb will be referred to again in the discussion of the treatment of Addison's disease.) Loeb subsequently verified these results in dogs, and his work has since been confirmed by Harrop and his associates.[18]

Harrop[18] found that stopping the injection of cortical extract in adrenalectomized animals in apparently good condition caused an immediate loss of sodium chloride before the excretion of nitrogen

17. (*a*) Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**:420 (Nov. 4) 1932; (*b*) Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, Proc. Soc. Exper. Biol. & Med. **30**:808 (March) 1933. (*c*) Loeb, R. F.; Atchley, Dana W.; Benedict, Ethel M., and Leland, Jessica: Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to the Excretion of Sodium, J. Exper. Med. **57**:775 (May) 1933.

18. Harrop, G. A.; Soffer, L. J.; Ellsworth, Read, and Trescher, J. H.: Studies on the Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, J. Exper. Med. **58**:17 (July) 1933.

was much affected. The daily excretion of sodium chloride rose to double the original value, although after resumption of the use of the extract the excretion of this substance again returned to its former level. As a result of their experiments Harrop and his associates concluded:

> A characteristic alteration in the electrolyte structure of the blood plasma of the suprarenalectomized dog occurs when injections of cortical extract are stopped. This alteration progresses during the course of the suprarenal insufficiency, parallel with the hemoconcentration and the loss in weight. When injections of cortical extract are resumed, the electrolyte structure returns to its original form, the alterations paralleling the dilution of the blood and the return of the body weight to its original level.
>
> The hemoconcentration, with the resulting physiological changes which take place in the suprarenalectomized dog after the cessation of cortical extract injections, is associated with a loss of sodium and chloride, accompanied by their proper complement of body water, by way of the kidney. Since this effect is produced in the suprarenalectomized animal, well nourished and in excellent condition, solely by cessation of injections of the cortical hormone, and since the reverse process of repair of the electrolyte and water losses can be effected solely by resumption of extract injections, it follows that all of the observed phenomena are due to this cause, and to this alone. It can be concluded that one function of the cortical extract in the suprarenalectomized dog is that of participation in the regulation of the sodium and chloride metabolism, and consequently, of the balance and distribution of water. The loss of water, in the absence of the cortical hormone, is sustained partly by the blood plasma, but to a far greater extent by the interstitial body fluid. The available evidence points to the kidney as the focus of this regulatory function of the cortical hormone.

Zwemer and Sullivan,[19] working with approximately 45 cats, investigated the chronological order of the changes in the chemical constituents of the blood which occur in cases of adrenal insufficiency and in general confirmed the work of Loeb and Harrop. They stated that adrenalectomy is followed by an early loss of sodium, reflected in a lowered carbon dioxide-combining power and in an increase in the values for potassium and nonprotein nitrogen of the blood. Chemically the syndrome of adrenal insufficiency seemed to Zwemer[20] to be a disturbance in the metabolism of salt and water, with loss of water and depletion of sodium and blood chlorides together with an increase of potassium in the blood. The injection of an extract of adrenal cortex into adrenalectomized animals was found to bring about a reversal of the chemical changes that occurred in animals with adrenal insufficiency, in addition to affecting the observable symptoms favorably. The suggestion was made that the adrenal cortex secretes something that enables the cells to metabolize salts and water.

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19. Zwemer, R. L., and Sullivan, R. C.: Blood Chemistry of Adrenal Insufficiency in Cats, Endocrinology **18**:97 (Jan.-Feb.) 1934.

20. Zwemer, R. L.: The Adrenal Cortex and Electrolyte Metabolism, Endocrinology **18**:161 (March-April) 1934.

Gilman [21] has presented the results of some very interesting experiments which demonstrate the effect in dogs of the loss of sodium without a concomitant loss of water or potassium. Using the method of Darrow and Yannet,[22] Gilman injected 100 cc. per kilogram of body weight of isotonic solution of dextrose into the peritoneal cavity of dogs. The solution then attained osmotic equilibrium with its surroundings. After six hours complete equilibration had taken place before there was appreciable absorption of fluid by the dextrose solution, which by this time was a protein-free fluid that had a composition almost identical with that of extracellular fluid and contained a large amount of sodium. The fluid was then withdrawn by paracentesis. By this ingenious method there was produced a loss of sodium into the peritoneal cavity which was not accompanied by a loss of fluid. Immediately after withdrawal of the fluid studies of the chemical constituents of the blood were made, and the animals were subjected to slight hemorrhage which lowered the blood pressure to shock level. It was found that a marked fall occurred in the concentration of sodium and in the osmotic pressure of the serum. A shift of water into the cells in order to maintain osmotic equilibrium resulted in marked depletion of the extracellular fluid, as evidenced in the circulation by an increase in the specific gravity of its serum and by a fall in the blood pressure. This was in marked contrast to the results obtained after bleeding normal dogs to this extent. The intravenous injection of a 30 per cent solution of sodium chloride to replace the amount of sodium lost produced dramatic effects: The blood pressure returned to normal and the animal recovered immediately from the symptoms of shock and was ambulatory in a few hours. Gilman concluded from the similarity of behavior between his animals and adrenalectomized dogs that a similar shift in water occurs in the latter and that this shift accounts for the circulatory phenomena observed in adrenal insufficiency.

While these investigations on the function of the cortical hormone were in progress, Kendall and his associates [23] were directing their efforts to a chemical study of the hormone itself. In April 1934 he and his associates announced the isolation from the adrenal cortex of a crystalline form of the hormone which was essential to life. Further

21. Gilman, Alfred: Experimental Sodium Loss Analogous to Adrenal Insufficiency: The Resulting Water Shift and Sensitivity to Hemorrhage, Am. J. Physiol. **108**:662 (June) 1934.

22. Darrow, D. C., and Yannet, H., quoted by Gilman.[21]

23. Kendall, E. C.; Mason, H. L.; McKenzie, B. F.; Myers, C. S., and Koelsche, G. A.: Isolation in Crystalline Form of the Hormone Essential to Life from the Suprarenal Cortex: Its Chemical Nature and Physiologic Properties, Proc. Staff Meet., Mayo Clin. **9**:245 (April 25) 1934. Kendall, E. C.: Suprarenal Cortical Hormone, Minnesota Med. **18**:71 (Feb.) 1935.

studies on the chemical formula and physiologic activities of this substance are in progress.

In the preceding paragraphs a brief summary of some of the work being done on the physiology of the cortex of the adrenal glands has been presented. It is important to bear in mind in evaluating this experimental work that considerable differences exist in the behavior of various species and even in members of the same species after adrenalectomy. For example, it has been possible to maintain some dogs in good health for long periods by the injection of saline solution alone. Other dogs react unfavorably almost immediately after the cortical hormone has been withdrawn. To make matters more complicated, there is likely to be marked variation in the potency of different batches of the extract, and, as Kendall [24] pointed out in discussing Harrop's work, extracts standardized on the behavior of dogs may show marked variations in potency. Furthermore, there is considerable evidence to suggest that the adrenal gland may elaborate other hormones which as yet have not been isolated, and the impure extracts that are used for experimental purposes may possibly contain variable amounts of these additional hormones.

ADDISON'S DISEASE

In 1855 Addison [25] described the disease which now bears his name. In his original description he gave as the characteristic symptoms "anemia, general languor or debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of color in the skin." One year later Claude Bernard [26] excised the adrenal glands of animals and thereby produced fatal symptoms which he thought resembled those of Addison's disease.[27] In subsequent years the observations of both men were confirmed repeatedly, but except for a sharper delineation of the symptoms and pathologic findings no advance of phenomenal importance was made in the diagnosis or treatment of Addison's disease for seventy-five years. During these years it was

24. Kendall, E. C.: Tr. A. Am. Physicians **49**:156, 1934.

25. Addison, Thomas: A Collection of the Published Writings of the Late Thomas Addison, London, The New Sydenham Society, 1868.

26. Bernard, Claude: Compt. rend. Acad. d. sc. **43**:422 and 542, 1856; J. de physiol. de l'homme **1**:160, 1858.

27. As Stewart [2a] correctly pointed out, much of the earlier work on the effects of bilateral adrenalectomy in animals proved nothing except that the experimenter was a poor surgeon. For example, Stewart, commenting on without criticizing the data of Brown-Séquard, showed beyond any doubt that when Brown-Séquard announced that the adrenal glands were indispensable to life his conclusion could not have been anything except a lucky guess. The same remark would have been equally applicable to the work of Claude Bernard, whose animals following the removal of one adrenal gland lived about twenty-five hours. Nevertheless, Claude Bernard deserves credit for starting the physiologic ball rolling.

definitely established that tuberculosis or atrophy of the adrenal glands accounted for most cases of the disease, that the morbidity of the disease was largely the result of destruction of the cortex and that the medulla and its hormone epinephrine were of secondary importance. Treatment was most unsatisfactory, though there appeared to be some promise of success in the Muirhead regimen which was sponsored by Rowntree and Snell.[1] Following the announcement of preparations of active hormones of the adrenal gland by Swingle and Pfiffner [8a] and by Hartman and Brownell [7a] there was a marked revival of interest in this disease; diagnostic procedures of considerable value have been developed, and satisfactory therapeusis appears to lie in the offing.

Symptoms.—Addison's [25] original and now classic description of the symptoms could scarcely be improved, and these symptoms are so well known that they can be dismissed without much comment.

It is important to bear in mind that the symptoms of the disease observed in the stage of crisis are distinctly different and should be sharply differentiated from those which appear during the stage of chronicity. In crisis the symptoms apparently result from an acute deficiency of the cortical hormone; in chronicity, the residual symptoms which persist after treatment, namely, slight weakness and asthenia, lowered resistance, hypotension and pigmentation, may be in part the result of medullary deficiency. In crisis, because of the preponderance of gastro-intestinal symptoms, such as nausea, vomiting, diarrhea and abdominal pain, the clinical picture may even simulate acute abdominal disease.[28] Hiccup may be the first indication of the onset of crisis, and its importance as a manifestation of Addison's disease is often overlooked. The frequency of digestive disturbances in Addison's disease has been the subject of a recent study by Marañón and Arguelles.[29]

Pathologic Physiology.—As a result of recent physiologic studies a closer correlation has been established between experimental adrenal insufficiency and Addison's disease. However, Addison's disease in its entirety has never been produced experimentally in laboratory animals.[30]

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28. I recall with great vividness a case in which an erroneous diagnosis of subacute cholecystitis was made. The patient, an inmate of a large general hospital, died during the course of an attempt to remove the gallbladder. At necropsy two large caseous adrenal glands were the only features of consequence observed.

29. Marañón, G.; Sala, P., and Arguelles, G.: Digestive Symptoms in Chronic Suprarenal Insufficiency (Addison's Disease), Endocrinology **18**:497 (July-Aug.) 1934.

30. Rogoff (Proc. Soc. Exper. Biol. & Med. **29**:1240 [June] 1932) by means of subtotal ligation of the adrenal vessels has attempted with some success to reproduce atrophy of the adrenal glands comparable to that which occurs in some cases of Addison's disease. Clinical symptoms of subacute or chronic adrenal insufficiency appeared in some animals. The author did not state whether or not pigmentation resulted.

Adrenalectomized animals can be kept in perfect health over an indefinite period by replacement therapy, supplemented possibly by the addition of a liberal amount of sodium chloride to the diet. These animals breed and lactate and to all intents and purposes seem entirely normal. In spite of the best treatment available at present, however, patients with Addison's disease are rarely entirely normal: Pigmentation exists, the blood pressure remains low, and they usually lack normal vigor and stamina.

The recognition of the relationship of the disturbance of the metabolism of electrolytes to adrenal insufficiency marks a distinct advance in the knowledge of the pathologic physiology of Addison's disease. The striking effects of Ringer-dextrose solution in prolonging the life of adrenalectomized animals beyond the expected period of survival were demonstrated as early as 1925 by Rogoff and Stewart,[31] and their results were confirmed by Banting and Gairns[32] in the following year. Using saline solutions alone, Marine and Baumann[33] obtained similar results in similar experiments. Furthermore, Baumann and Kurland[34] noted a decrease of as much as 15 per cent in the sodium content of the blood of adrenalectomized rabbits. Clinicians were also aware of the therapeutic value of administering saline and dextrose solutions in the treatment of the "dehydration" that occurred during crises of Addison's disease. Although these facts were known, they excited little interest or comment until their significance was appreciated and demonstrated by Loeb and Harrop. Loeb[17a] reported complete analyses of the inorganic base in the serum of 3 patients. In all 3 there was marked reduction in the values for sodium and the chlorides and an increase in the content of potassium in the serum. These chemical values were also studied in adrenalectomized dogs,[17c] and these animals were found in periods of adrenal insufficiency to excrete an abnormal amount of sodium in the urine and to show a corresponding reduction in the values for sodium and chlorides in the serum. Harrop,[18] working independently, also found in adrenalectomized animals that the total base of the blood serum

31. Stewart, G. N., and Rogoff, J. M.: Studies on Adrenal Insufficiency, Proc Soc. Exper. Biol. & Med. **22**:394 (April) 1924-1925. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency: VIII. The Survival Period of Untreated Adrenalectomised Cats, Am. J. Physiol. **88**:162 (Feb.) 1929.

32. Banting, F. G., and Gairns, S.: Suprarenal Insufficiency, Am. J. Physiol **77**:100 (June) 1926.

33. Marine, David, and Baumann, E. J.: Duration of Life After Suprarenalectomy in Cats and Attempts to Prolong It by Injections of Solutions Containing Sodium Salts, Glucose, and Glycerol, Am. J. Physiol. **81**:86 (June) 1927.

34. Baumann, E. J., and Kurland, Sarah: Changes in the Inorganic Constituents of Blood in Suprarenalectomized Cats and Rabbits, J. Biol. Chem. **71**:281 (Jan.) 1927.

was reduced largely at the expense of sodium and that the values for serum calcium, potassium and magnesium were increased.

Proof of the relationship between the sodium content of the serum and adrenal insufficiency was finally established by Loeb,[17a] who gave a patient with Addison's disease additional salt by mouth. Marked improvement in the clinical condition took place. The administration of salt was then stopped because of the appearance of edema under the eyes, and five days later the patient was precipitated into a typical addisonian crisis. Studies of the total base of the serum showed the sodium content to be reduced. The administration of sodium chloride, even though no cortical hormone was given, brought about prompt improvement in the patient's condition, and the values for the electrolytes of the blood became normal. These results have since been confirmed by Harrop and his associates,[35] so that it is reasonably well established that the abnormal behavior of the serum electrolytes is of fundamental significance in the pathologic physiology of Addison's disease and that this abnormality in patients is manifested during periods of relapse or crisis by a decreased concentration of the sodium and chloride ions in the serum, a decreased concentration of the titratable total base and an increase in the concentration of the potassium ions. The values for calcium and magnesium are increased or unchanged.

The cause of the pigmentation that occurs with great regularity in Addison's disease is still a mystery. It is known that the pigmentation results from the deposition of an abnormal amount of melanin, which is the normal pigment of the skin. The metabolism of melanin is still unexplored. Snell and Rowntree [36] reviewed the literature on the subject in 1929. The various theories were reviewed at that time, and since the article was written no contributions of note have come to my attention. Harrop and his collaborators [35] as well as many of the earlier writers, thought that pigmentation may be a manifestation of medullary insufficiency.

Pathology.—It is generally stated that tuberculosis of the adrenal glands accounts for from 80 to 90 per cent of cases of Addison's disease. Atrophy of these glands explains the vast majority of the remainder. It is interesting to note that this ratio seems to be changing. Snell [37] stated that: "A search of the literature revealed that in seventeen of the thirty recently reported necropsies, in cases of Addison's

35. Harrop, G. A.; Weinstein, Albert; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850 (June 10) 1933.

36. Snell, A. M., and Rowntree, L. G.: Addison's Disease with Anomalous Pigmentation, Endokrinologie **5**:303, 1929.

37. Snell, A. M.: The Treatment of Addison's Disease, Proc. Staff Meet., Mayo Clin. **9**:57 (Jan. 24) 1934.

disease which had been treated, atrophy of the suprarenal glands was present." According to these figures atrophy of the adrenal glands accounted for 57 per cent of the cases in which patients died and came to necropsy. As there is no good reason to presume that the adrenal glands are now being attacked by tuberculosis less frequently than in former years it would appear either that treatment is more effective in prolonging life in the group of patients whose condition is caused by adrenal tuberculosis or that these patients may be "protected to some extent by the survival of fragments of cortical tissue and cortical adenomas." [37] The tuberculous process appears to start either in the medullary or in the midcortical portion and then to advance toward the periphery. Adenomas of the cortex may or may not be involved. Presumably those adenomas that remain may have the capacity to function. In contradistinction to the tuberculous process, atrophy begins in the cortex and compresses the medulla. Fragments of medullary tissue may remain, but usually the entire gland is destroyed. The cause of the atrophy is entirely unknown. Occasionally Addison's disease is reported as being caused by extra-adrenal disease. A recent example was a case reported by Bicknell [38] in which malignant involvement of the solar plexus was found. Tuberculosis of the adrenal glands has been studied recently by Gsell and Uehlinger.[39] Thirty-five cases of bilateral total tuberculosis and 37 of unilateral or bilateral incomplete tuberculosis were analyzed. These writers concluded that the infection is hematogenous and originates in a primary or postprimary tuberculous focus. In a third of their cases the only active tuberculous process was in the adrenal glands. They stated that the infection probably begins during or after puberty and has a long period of development, during which the disease proceeds intermittently, the symptoms of Addison's disease beginning only after the period of glandular insufficiency. Barker [40] has made an excellent study of the pathologic anatomy of Addison's disease, and a comprehensive survey of the entire field of adrenal pathology, including tumors, may be found in the article by Fritz Paul.[41]

Diagnosis.—The diagnosis of a typical case of Addison's disease usually presents no difficulties. In doubtful cases, especially in those in

38. Bicknell, Franklin: Addison's Disease Due to Malignant Involvement of the Solar Plexus, Brit. M. J. **2**:206 (Aug. 4) 1934.

39. Gsell, O., and Uehlinger, E.: Tuberkulöser Morbus Addison. Stellung der Nebennierentuberkulose im Ablauf der tuberkulösen Infektion, Beitr. z. Klin. d. Tuberk. **83**:121, 1933.

40. Barker, N. W.: The Pathologic Anatomy in Twenty-Eight Cases of Addison's Disease, Arch. Path. **8**:432 (Sept.) 1929.

41. Paul, Fritz: Die krankhafte Funktion der Nebenniere und ihr gestaltlicher Ausdruck, Virchows Arch. f. path. Anat. **282**:256 (Oct. 17) 1931.

which there is no pigmentation, three procedures have proved to be of distinct value: 1. Biopsy of the skin may be of material aid in excluding other causes of pigmentation, such as those produced by arsenic, silver, hemachromatosis and acanthosis nigricans. Biopsy, however, will not positively identify the pigmentation of Addison's disease as such. 2. Camp, Ball and Greene [42] were able to identify calcium in the adrenal glands by making roentgenograms with the patient in the oblique position.[43] Positive findings were disclosed in a series of 6 of 23 consecutive patients. In interpreting such roentgenograms it is important that one be not misled by calcification of the adjacent lymph nodes or cartilages of the ribs. Apparently normal persons occasionally present roentgenographic findings corresponding with those seen in Addison's disease. It is not known whether adrenal insufficiency will or will not subsequently develop in such persons. 3. Harrop and his associates [35] suggested the use of a salt-free diet to aid in the diagnosis of Addison's disease. In normal persons with intact adrenal glands no symptoms result from deprivation of salt, and only minor changes occur in the chemical constitution of the blood. However, in a patient with Addison's disease this deprivation is almost certain to precipitate a state of "acute relapse," with its attendant blood picture of acute adrenal insufficiency. The value of this test has been observed at the Mayo Clinic in several cases. In one patient, under observation at the present time, pigmentation was so slight that one could not be sure of its presence. Evidence of calcification was absent in roentgenograms of the adrenal areas. Fifty-four hours after the patient was placed on a salt-free diet the diagnosis of Addison's disease was definitely established. This test when used in conjunction with roentgenographic studies of the adrenal areas should be of great value, not only in cases in which pigmentation is lacking, but also in cases in which the patient is a member of one of the darker skinned races, in whom the presence of pigmentation is notoriously difficult to evaluate. It is important to call attention to the fact that this diagnostic procedure is not without considerable danger and should not be undertaken unless the physician is familiar with the signs and symptoms of acute adrenal insufficiency and has at hand a liberal supply of the cortical hormone and the means of administering treatment promptly should the symptoms of crisis appear.

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42. Camp, J. D.; Ball, R. G., and Greene, C. H.: Calcification of the Suprarenal Glands in Addison's Disease: Roentgenographic Study, Am. J. Roentgenol. **28**:594 (Nov.) 1932.

43. As early as 1914 Rolleston and Boyd (Rolleston, H. D., and Boyd, E. J.: Brit. J. Child. Dis. **11**:105 [March] 1914) detected calcification in the adrenal glands by roentgenographic methods. The technic was perfected by Camp and his associates.

Treatment.—It is unfortunate that at present there is no method by which minor degrees of adrenal cortical insufficiency can be measured. On that account the treatment of Addison's disease is still somewhat crude and comparable to what the treatment of diabetes would be without methods for determining the sugar content of the urine and blood. Theoretically the treatment should be simple, and it should consist essentially in supplying the missing hormone and maintaining the normal chemical pattern of the blood. In practice these aims are partially accomplished by the injection of cortical hormone and by the use of additional salt in the diet. Recently the value of commercial preparations of the hormone has been vigorously challenged by Rogoff,[44] and there is considerable difference of opinion regarding the relative merits of the use of sodium chloride and the hormone. It is difficult to reconcile Rogoff's views with present clinical experience and with the earlier reports of the efficacy of the cortical hormone.[45] When those reports were written it was generally thought that the value of cortical hormone in the treatment of Addison's disease had been established. It is important to bear in mind that the poor results which Rogoff reported were obtained with commercial extracts. There seems to be no doubt of the fact that different lots of the available commercial preparations may vary in potency; and it is unfortunate that such is the case. The fault, however, appears to lie not with the hormone itself but with methods of preparing and standardizing it. Until some simple and rapid method of measuring cortical adrenal activity is available it appears likely that there will be trouble in preparing standard potent extracts. Cantor and Scott [46] recently reported a case which illustrates the value of the hormone. Their patient was revived from a state of crisis no less than fourteen times in twenty-six months by its use.

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44. Rogoff, J. M.: The Adrenal Cortical Hormone: Experiments with a Commercial Adrenal Extract (Eschatin), J. A. M. A. **103**:1764 (Dec. 8) 1934.

45. Rowntree, L. G.; Greene, C. H.; Swingle, W. W., and Pfiffner, J. J.: The Treatment of Patients with Addison's Disease with the Cortical Hormone of Swingle and Pfiffner, Science **72**:482, 1930; Addison's Disease: Experiences in Treatment with Various Suprarenal Preparations, J. A. M. A. **96**:231 (Jan. 24) 1931. Rowntree, L. G.; Greene, C. H.; Ball, R. G.; Swingle, W. W., and Pfiffner, J. J.: Treatment of Addison's Disease with the Cortical Hormone of the Suprarenal Gland: Summary of Immediate Results in Twenty Cases Treated with the Preparation Made by Swingle and Pfiffner, ibid. **97**:1446 (Nov. 14) 1931. Swingle, W. W., and Pfiffner, J. J.: The Adrenal Cortical Hormone, Medicine **11**:371 (Dec.) 1932. Hartman, F. A.: Studies on the Function and Clinical Use of Cortin, Ann. Int. Med. **7**:6 (July) 1933.

46. Cantor, M. M., and Scott, J. W.: Treatment of Addison's Disease with an Extract of the Adrenal Gland: Report of a Case in Which Experimental Relapses and Remissions Were Brought About, Endocrinology **18**:341 (May-June) 1934.

Largely as the result of the investigations of Loeb and Harrop the place of sodium chloride has been definitely established in the treatment of Addison's disease. Harrop and his associates [35] reported the cases of 4 patients with the disease in its chronic phase who were able to remain in reasonably good health by the addition of sodium chloride to their diet. These patients were not given the hormone. As a result of previous experience with cases in which patients were treated with the hormone alone, Harrop and his associates were led to believe that the clinical value of injections of cortical hormone during periods of remission had not been demonstrated. They observed no effect on the hypotension or pigmentation and were not convinced of the efficacy of the hormone in maintaining nutrition and weight; however, they saw no danger in its use. They felt that its chief value was in the treatment of the patient in a state of acute relapse, when its use was of definite help and might be of vital importance.

Snell [47] has recently reviewed the treatment of Addison's disease with sodium chloride and cortical hormone. He emphasized the necessity for individualizing treatment and pointed out the well established fact that treatment of the patient either in a state of crisis or in one bordering on crisis is considerably different from that used during periods of latency. The treatment of a patient in a state of acute relapse, according to Snell, is of the same magnitude and importance as the treatment of a patient with diabetic acidosis or coma. Cortical hormone is unquestionably necessary here and should be given preferably in small repeated doses rather than in one large dose. From 5 to 20 cc. or more should be given intravenously or intramuscularly; in the presence of acute infection larger doses may be necessary. The intravenous administration of physiologic solution of sodium chloride and solutions of dextrose, Snell stated, is an almost indispensable adjunct. After the patient has been brought out of a state of crisis, further treatment should depend on his condition and the level of the blood chlorides and blood urea. He pointed out that most, if not all, of the failures in the treatment of crisis may be attributed to the administration of an insufficient amount of hormone. He recognized that some patients can get along with salt alone; from 6 to 15 Gm. of salt is added to the diet, which may be given in enteric-coated capsules. (Since his article has been published, it has been the practice at the Mayo Clinic to give sodium chloride by mouth in the form of a physiologic solution. Salt also may be given in milk or with lemon juice. Enteric-coated capsules are expensive and in some cases cause gastro-intestinal disturbances.) Other patients do better

47. Snell, A. M.: The Diagnosis and Treatment of Addison's Disease with Reference to a Series of Forty-Six Patients Treated with the Suprarenal Cortical Hormone, Internat. Clin. **3**:46 (Sept.) 1934.

on a regimen of sodium chloride plus small amounts of hormone. Snell pointed out the advisability of determining the necessity for use of the hormone before the patient is dismissed from the hospital, and he stressed the necessity of instructing such a patient regarding the dangers of crisis and the need of prompt and energetic treatment should relapse occur.

(Experience in 3 cases observed at the Mayo Clinic, reports of which have not yet been published, indicates that in certain instances at least continued use of the hormone is as necessary as the use of saline solutions. One of the patients was very sensitive to withdrawal of the hormone, even though the use of salt was continued. When administration of the hormone was discontinued anorexia, abdominal pain and asthenia developed, and these symptoms were relieved only by injection of the hormone.)

Wilder [48] recently published observations indicating that extracts of the anterior lobe of the pituitary body might be of some value in the treatment of Addison's disease. One patient, who remained in the state of invalidism in spite of the use of cortical hormone and saline solution, received considerable benefit, as shown by a gain in weight and strength when extract of the anterior lobe of the pituitary gland was added to the treatment. Other patients seem to be less sensitive to deprivation of salt while receiving the pituitary extract. This adjunct to treatment is based on the work of Kraus,[49] who observed regressive changes in the chromophil cells in the pituitary body in cases of Addison's disease.

Most experienced clinicians would probably agree that the general principles underlying the present treatment of Addison's disease could be summarized as follows:

1. The patient in a state of crisis is not likely to be overtreated. In such instances large amounts, from 10 to 50 cc. or more of the hormone, should be used in conjunction with saline solution given, if necessary, intravenously. The dose should be increased until an effect is achieved.

2. No hard and fast rule can be laid down for the treatment of the patient in the stage of chronicity. Many patients apparently get along satisfactorily with the aid of additional salt in the diet. In many such cases the use of small daily doses of the hormone (2 cc., for example) is unnecessary. However, such small doses probably do no harm except to deplete the patient's pocketbook.

3. The use of the hormone in its present form should as a rule be restricted to those patients who are in a state of crisis and to those

48. Wilder, R. M.: The Use of Anterior Lobe Pituitary Extract in the Treatment of Addison's Disease, Proc. Staff Meet., Mayo Clin. **9**:689 (Nov. 14) 1934.

49. Kraus, E. J.: Zur Pathologie des Morbus Addisoni (Befundi in Hypophyse und Nebennieren), Beitr. z. path. Anat. u. z. allg. Path. **78**:283, 1927.

occasional patients who cannot get along without the hormone and who are in a state that has been termed "chronic relapse."

4. The general condition of the patient and the status of the blood chlorides and blood urea can be used as a guide in management. A consideration of the changes in the weight of the patient is of great importance. Loss of weight can never be safely disregarded, and a patient who is adequately treated should gain weight or at least maintain his weight at a constant level.

Results of Treatment.—To evaluate the results of treatment it is necessary to bear in mind the fact that some patients who are not treated live for a remarkably long time. Snell [50] recently reported a case in which pigmentation was first noticed in 1917 and a definite positive diagnosis of Addison's disease was made in 1923. In a study of 566 cases reported in the literature prior to 1929, Guttman [51] found that the average length of life of patients with Addison's disease caused by atrophy of the adrenal glands was 34.02 ± 4.4 months and that the average duration of the disease caused by tuberculosis of the adrenal glands was 13.315 ± 2.55 months. It is obvious that an insufficient length of time has passed to evaluate the results of treatment with present methods.

Lisser, Taylor and Leet [52] reviewed the results of the use of cortical extracts in 100 cases. Three of the patients in this series were their own. They expressed the belief that a thorough clinical trial of the efficacy of cortical hormone must await its further concentration and purification. They commented on the magic effects following administration of cortical extract to patients in a state of crisis. The authors' 3 patients died because of the administration of inadequate amounts of the hormone. The authors commented on the high cost of the extracts and concluded that the purchase of an adequate amount would mean an annual expenditure of from $500 to $1,500 per patient. It is obvious that only the rich can afford to have Addison's disease.

Results of treatment were reviewed by Harrop and his associates [35] in June 1933. They treated 13 patients over a period of two and a half years. Of these 13 patients, 7 died. One patient died as a result of inadequate treatment and 2 patients had advanced tuberculosis elsewhere in the body. In the remaining 4 cases suprarenal cortical atrophy

50. Snell, A. M.: Addison's Disease of Unusually Long Duration, Proc. Staff Meet., Mayo Clin. **9**:303 (May 23) 1934.

51. Guttman, P. H.: Addison's Disease: A Statistical Analysis of Five Hundred and Sixty-Six Cases and a Study of the Pathology, Arch. Path. **10**:742 (Nov.); 895 (Dec.) 1930.

52. Lisser, H.; Taylor, F. B., and Leet, N. B.: The Adrenal Cortical Therapy of Addison's Disease in Clinical Practice, Endocrinology **18**:333 (May-June) 1934.

was present. The patients who were living had had the disease from four to sixteen months and were in reasonably good health. Snell,[37] in January 1934, reported the results of treatment in 48 patients with Addison's disease seen at the Mayo Clinic from May 1930 to January 1934. Thirty-two patients had died, 12 of whom received what was thought to be adequate treatment. Sixteen patients were living; of these, 7 were in good condition for more than a year, 6 were reported as doing well although treatment had been in progress for less than six months, and 3 were in poor condition because of their inability to obtain adequate supplies of the hormone.

It is evident from these reports that the treatment of Addison's disease still leaves much to be desired so far as the expectancy of life is concerned. Nevertheless, the sense of well-being, the increased vigor and the improvement in the mental status of the patient make treatment worth while. It seems likely that better results will be achieved in the near future as a result of improved methods of treatment and more refined preparation of the hormone.

DISEASES CHARACTERIZED BY CORTICAL OR MEDULLARY HYPERFUNCTION

It will be recalled that the adrenal gland consists of two portions which differ in origin, structure and function. The cortex or outer portion arises from the embryonic buds of celomic epithelium that project from the region of the root of the mesentery into the mesenchyma mesial to the wolffian bodies. From the mesial side of the wolffian bodies the undifferentiated primitive sex glands take their origin and after further development become differentiated into ovaries or testes and subsequently descend to the pelvis or scrotum. The intimate embryologic relationship of the adrenal cortex and sex glands assumes importance because adrenal cortical tumors usually are associated with changes in the secondary sexual characteristics. The medullary portion of the adrenal gland takes its origin in the mass of cells that arise from the abdominal portion of the sympathetic nervous system. At the end of the first month of fetal life the strands of these cells penetrate into the adrenal cortex where they become concentrated and after further differentiation lose their resemblance to nerve cells and form the adult suprarenal medulla.

When classified functionally the following disturbances in the adrenal glands are theoretically possible: (1) cortical hyperfunction, (2) cortical hypofunction, (3) medullary hyperfunction and (4) medullary hypofunction. One can conceive of mixed clinical pictures in which hyperfunction of the cortex could be associated with hypofunction of the medulla and vice versa, but as yet no clearcut clinical examples of

this have been described. Three of the four theoretical possibilities have been encountered clinically, namely, cortical (and medullary?) insufficiency, which is exemplified by Addison's disease; medullary hyperfunction, which is seen in the hyperfunctioning medullary tumors, such as paraganglioma or pheochromocytoma, that produce paroxysmal hypertension or continuous hypertension often indistinguishable from essential hypertension, and finally, cortical hyperfunction, which is presumed to produce the so-called adrenal cortical syndrome. This syndrome has been called by various writers suprarenal virilism, the genitosuprarenal syndrome, adrenal hirsutism, *le syndrome génito-surrénal* and other similar names. None of these terms is entirely satisfactory. In this paper we shall speak of it as the adrenal cortical syndrome.

Symptoms in the Adrenal Cortical Syndrome.—The symptoms vary depending on the age and sex of the patient and the nature of the pathologic process in the adrenal glands. Unquestionably it occurs in males, although in the majority of cases reported the patients have been female. Before puberty the disease is characterized in boys by precocious somatic and sexual development. Lisser [53] recently reviewed the literature on cortical adrenal tumor in boys and found 8 unquestionable cases and 2 additional cases in which the disease probably was present. Lisser reported a ninth case in which a boy aged 4 years had a bone age of a child of 12 years, the genitalia of a man and semen-containing spermatozoa. Diagnosis was made by roentgenograms, and a tumor of the left adrenal gland was successfully removed. Amelioration of the symptoms resulted. In 1927, Gordon and Browder [54] reported a similar case; at necropsy carcinoma of the left adrenal gland was found. Unfortunately, in this case the pituitary body was not examined. The disease occurs much less frequently in men. A few cases, however, have been reported, notably by Weber,[55] Holl [56] and Broster and Vines.[57] In these cases there seemed to be a definite degree of feminization, resulting in a female type of obesity associated with well developed breasts which were

53. Lisser, H.: Successful Removal of Adrenal Cortical Tumor Causing Sexual Precocity, Tr. A. Am. Physicians **48**:224, 1933.

54. Gordon, M. B., and Browder, J. E.: Suprarenal Carcinoma with Pubertas Praecox in a Boy Three Years of Age, Endocrinology **11**:265 (July-Aug.) 1927.

55. Weber, F. P.: Cutaneous Striae, Purpura, High Blood-Pressure, Amenorrhoea and Obesity, of the Type Sometimes Connected with Cortical Tumours of the Adrenal Glands, Occurring in the Absence of Any Such Tumour—With Some Remarks on the Morphogenetic and Hormonic Effects of True Hypernephromata of the Adrenal Cortex, Brit. J. Dermat. **38**:1 (Jan.) 1926.

56. Holl, Gundakr: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, Deutsche Ztschr. f. Chir. **226**:277, 1930.

57. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Company, Ltd., 1933.

capable of secreting milk. In some instances loss of libido and atrophy of the penis and testes were present. In girls before the age of puberty, obesity, premature sexual development and menstruation, enlargement of the breasts, hypertrophy of the clitoris and hirsutism are the usual symptoms. Representative cases in which a cortical tumor was successfully removed have been reported by Collett [58] and by Kennedy and Walters.[59]

In the majority of cases the disease occurs in women and is characterized by an abnormal growth of hair of masculine distribution, amenorrhea, profound weakness, hypertension, peculiar swelling and high color of the face and often diabetes, which may be either latent or frank. Other symptoms, such as purplish striae of the skin, osteoporosis and such psychologic changes as loss of modesty and lack of interest in the male sex have been noted. Considerable variation in the presence and intensity of these symptoms may occur.

Symptoms may appear with surprising rapidity. In 1 case the face became so swollen within a period of three weeks that acute nephritis was suspected. Usually, however, the onset is more gradual, and it is only after the lapse of several months or longer that the change in the appearance of the patient becomes marked. Generally there is gain in weight, although in some cases reported this gain has not been marked, and the patient does not necessarily become obese. Likewise, the amount of hirsutism has been variable. In some cases the growth of hair on the face has been comparatively inconspicuous, and in others a fully developed beard has been present. Weakness, anorexia, hypertension and acne may be mild or absent.

Pathologic Findings.—Hyperfunctioning tumor of the adrenal cortex is present in the majority of cases of the adrenal cortical syndrome. In some cases the syndrome seems to be the result of unilateral or bilateral cortical hyperplasia and, finally, in a most interesting group of cases the syndrome has been present in disease of other glands of internal secretion, in which instances hyperplasia of the adrenal cortex has often been present.

Hyperfunctioning Cortical Tumors.—The older literature on the subject has been thoroughly reviewed by Glynn,[60] Bulloch and

58. Collett, Arthur: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:204 (March) 1924.

59. Kepler, E. J.; Kennedy, R. L. J.; Davis, A. C.; Walters, Waltman, and Wilder, R. M.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, Proc. Staff Meet., Mayo Clin. **9**:169 (March 21) 1934.

60. Glynn, E. E.: The Adrenal Cortex, Its Rests and Tumours: Its Relation to Other Ductless Glands, and Especially to Sex, Quart. J. Med. **5**:157 (Jan.) 1912.

Sequeira,[61] Collett,[58] Gallais,[62] Apert,[63] Holmes, [64] Rowntree and Ball [65] and other writers. More recently, cases have been reported by Cecil,[66] Lesher,[67] Hicks [68] and Kolodny.[69] In Kolodny's case the tumor which was situated between the leaves of the mesentery was successfully removed. Death occurred, however, from metastasis. When the adrenal cortical syndrome is present and associated with a tumor of the adrenal cortex the relation of the symptoms to the tumor appears to be clearcut. If the tumor is removed successfully regression of symptoms takes place, and in 1 case at least, reported by Walters and me,[59] recurrence of the tumor was followed by recurrence of the symptoms in all essential features.

Cortical Hyperplasia.—Here the relationship of the pathologic findings to the clinical picture is by no means so clearcut as in the case of adrenal tumor. Diffuse hyperplasia of the adrenal gland may occur as an accidental finding in cases in which there is no evidence of any endocrine disorder. Cortical hyperplasia unquestionably accounts for the adrenal cortical syndrome in some cases. This was exemplified indisputably in a case reported by Davis and Walters [59] in which death occurred, and gross and microscopic examination of the entire endocrine system disclosed no other pathologic changes. Goldzieher [70] has reported cases in which a number of salient features of the adrenal cortical syndrome were present and were relieved by unilateral or partial bilateral adrenalectomy. The diagnosis in some of these cases is not clearcut, and it cannot be said with certainty that the pathologic changes were confined to the adrenal glands. It may be possible that such cases represent a milder degree or an incomplete form of cortical hyperfunction.

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61. Bulloch, William, and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **41**:189, 1905.

62. Gallais, Alfred: Le syndrome génito-surrénal; étude anatomo-clinique, Paris, Société de pédiatrie de Paris, 1912.

63. Apert, E.: Dystrophies en relation avec des lésions de capsules surrénales; hirsutisme et pregeria, Bull. Soc. de pédiat. de Paris **12**:501, 1910.

64. Holmes, Gordon: A Case of Virilism with a Suprarenal Tumor: Recovery After Its Removal, Quart. J. Med. **18**:143, 1925.

65. Rowntree, L. G., and Ball, R. G.: Diseases of the Suprarenal Glands, Endocrinology **17**:263 (May-June) 1933.

66. Cecil, H. L.: Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, J. A. M. A. **100**:463 (Feb. 18) 1933.

67. Lesher, F. G.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Cortico-Genital Syndrome, Quart. J. Med. **4**:23 (Jan.) 1935.

68. Hicks, J. B.: Adenoma of the Adrenal Cortex (with Report of a Case), New England J. Med. **199**:1140 (Dec. 6) 1928.

69. Kolodny, Anatole: Suprarenal Virilism in a Woman (Tumor of an Extrarenal Suprarenal Rest), J. A. M. A. **102**:925 (March 24) 1934.

70. Goldzieher, M., and Koster, H.: Adrenal Cortical Hyperfunction, Am. J. Surg. **27**:93 (Jan.) 1935.

Broster and Vines [71] have recently written a monograph on the adrenal cortex and its relation to intersexuality. After presenting a résumé of the signs and symptoms of the adrenal cortical syndrome they classified the syndrome as follows: (1) adrenal pseudohermaphroditism, which is the most complete form of the disease and develops in utero before sex organs have become differentiated; (2) adrenal virilism, which develops after puberty and is characterized by alteration in the form of the body and external sex organs, hypertrichosis of the male type and disturbances of sexual function, and (3) Achard-Thiers syndrome or the "diabetes of bearded women," which is a condition usually found at necropsy and consists essentially of adrenal hyperplasia associated with changes in the other ductless glands. They recommended unilateral adrenalectomy as a treatment for adrenal virilism, the results of which have been disappointing in the other two groups. They reported 10 cases of adrenal virilism. The ages of the patients varied from 15 to 29 years. All were treated by unilateral adrenalectomy with beneficial results. Broster and Vines stated that the microscopic evidence of hyperfunction of the adrenal glands can be demonstrated by the Ponceau-Fuchsin staining reaction even in the absence of gross or microscopic evidence of hyperplasia. This reaction was positive in all 10 cases and was found to be negative in normal adrenal glands. If this work can be confirmed it unquestionably marks a distinct advance in the study of adrenal pathology. It is difficult to correlate Broster and Vines' results with the well known physiologic fact that unilateral adrenalectomy in animals is without any demonstrable effect. However, adrenal virilism may be comparable to exophthalmic goiter, which is often benefited by removal of one lobe of the thyroid gland.

The adrenal cortical syndrome may occur with bilateral adrenal cortical hyperplasia in association with disease of other glands of internal secretion, notably of the pituitary and the thymus. For example, in the syndrome which has been described by Cushing [72] as pituitary basophilism and which in its clinical features if not identical at least has many points in common with the cortical adrenal syndrome, the cortexes of the adrenal glands are frequently hypertrophied and may contain adenomas. It is possible in such cases that the hyperfunctioning baso-

71. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Company, Ltd., 1933, p. 94.

72. Cushing, Harvey: (*a*) The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**:137, 1932. (*b*) "Dyspituitarism": Twenty Years Later, with Special Consideration of the Pituitary Adenomas, Arch. Int. Med. **51**:487 (April) 1933. (*c*) Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

philic tumor of the pituitary body might stimulate overactivity of the adrenal cortex. There is some experimental work to indicate that such might be the case. For example, Evans,[73] Collip and his associates,[74] and Houssay[75] have independently presented evidence indicating the existence of an adrenotropic hormone. Houssay, for instance, demonstrated that in hypophysectomized dogs the weight of the adrenal glands decreased 38 per cent and was associated with atrophy and vacuolar degeneration of the cortex and that the administration of an extract of the anterior lobe produced marked hypertrophy of the cortex. Evans concluded from the evidence which he had obtained that the adrenal cortical tissue needs for its normal function some constituent of the anterior lobe of the pituitary gland. However, this experimental work does not prove that hyperfunctioning basophilic tumors of the pituitary body stimulate hyperfunction of the adrenal cortexes. The possibility that the adrenal gland is the chief offender and that pituitary disturbance is a secondary manifestation can also be entertained.

The adrenal cortical syndrome has likewise been found in cases of malignant tumor of the thymus when the latter is associated with bilateral hyperplasia of the adrenal cortex. Leyton, Turnbull and Bratton[76] reported 2 such cases. The appearance of 1 of these patients was so typical of pituitary basophilism that Cushing,[72c] in referring to the case, ventured the opinion that further search of the pituitary body would demonstrate the presence of a basophilic adenoma. Acting on Cushing's suggestion Turnbull made serial sections of the pituitary body, and no basophilic tumor was found. A similar case was reported by me.[77] In this case the resemblance to pituitary basophilism was not so striking as in one of the cases described by Leyton, Turnbull and Bratton. Nevertheless, most of the salient features of pituitary basophilism, including osteoporosis, as described by Cushing, were present. At necropsy the chief findings were bilateral cortical hyperplasia of the adrenal glands and a thymoma. It is significant that in this case, as in a similar case in which the patient is still living and which was reported

73. Evans, H. M.: Anterior Pituitary Function, J. A. M. A. **101**:425 (Aug. 5) 1933.

74. Collip, J. B.; Anderson, E. M., and Thomson, D. L.: The Adrenotropic Hormone of the Anterior Pituitary Lobe, Lancet **2**:347 (Aug. 12) 1933. Collip, J. B.: William Henry Welch Lectures: Some Recent Advances in the Physiology of the Anterior Pituitary, J. Mt. Sinai Hosp. **1**:28 (May-June) 1934.

75. Houssay, B. A.: A Series of Lectures on the Hypophysis, J. A. M. A. **101**:1167 (Oct. 7) 1933.

76. Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus with Pluriglandular Disturbance, J. Path. & Bact. **34**:635 (Sept.) 1931.

77. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases with Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **9**:402 (July 3) 1934, case 2.

by Walters, Wilder and me,[78] there was a marked reduction in the concentration of blood chlorides associated with a marked increase in the carbon dioxide-combining power of the blood. This alkalosis and reduction of the blood chlorides were not the result of vomiting and diarrhea or of any of the other factors that usually produce this chemical disturbance, and consequently there is reason to suspect that it may have been due to adrenal dysfunction as well as to adrenal cortical hyperfunction. Leyton [79] recently reviewed these cases and 1 or 2 others and pointed out that the syndrome of pituitary basophilism need not necessarily be the result of basophilic tumor of the pituitary body.

A most important case has been described by Lesher.[67] In this case all of the cardinal, and most of the occasional, symptoms and signs ascribed by Cushing to adenoma of the basophil cells of the pituitary body were present. A roentgenogram of the left kidney revealed a low position of the kidney and a calcified shadow above it. The patient was operated on by Mr. Gerald Dyke, who removed a cortical cell carcinoma of the left adrenal gland. The patient died about twelve hours after the operation. At necropsy, examination of serial sections of the pituitary body revealed a slight increase in the basophil and acidophil cells, and at one point there was a small collection of basophil cells 0.3 mm. in diameter. No significant pathologic abnormalities were found in the thyroid gland, parathyroid glands, pancreas or uterus. The ovaries were atrophic. Lesher made the following statement:

> In view of the case report in this patient and one or two others of a somewhat similar kind from the literature, it must be concluded that Cushing's syndrome, complete in its entirety, may be caused by such diseases as tumor of the suprarenal cortex, and so a clinical distinction cannot always be made between these two syndromes. Every case of Cushing's syndrome should be critically examined, including an x-ray examination of the abdomen for a shadow in the renal areas and for the position of the kidneys. Whilst it is generally accepted that the anterior lobe of the pituitary elaborates one or more gonadotropic secretions, there is no reliable evidence to show that the basophile cells are responsible for this. What evidence there is, is rather against this theory.

Diagnosis.—In a case in which the disease is well developed the clinical picture is so striking that it is easy to recognize that a given patient belongs to the large group having a condition often designated as a polyglandular or multiglandular syndrome. The facies, the peculiar distribution of fat, the unusual growth of hair and the history are typical. At present, however, it may be exceedingly difficult, if not altogether impossible, to differentiate with any degree of certainty pitui-

78. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases with Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **9**:400 (July 3) 1934, case 1.

79. Leyton, Otto: Multiglandular Disease (Schorstein Lecture), Lancet **1**:1221 (June 9) 1934.

tary basophilism, hyperfunctioning adrenal cortical tumor, bilateral adrenal cortical hyperplasia with or without thymoma and arrhenoblastoma of the ovary. Laboratory studies thus far have yielded no constant diagnostic feature. Roentgenographic studies of the head and determination of the fields of vision may be of little value because basophilic tumors of the pituitary body are frequently so small that they can be demonstrated only at necropsy after the pituitary body is examined microscopically by serial section. In cases of pituitary basophilism obesity is confined largely to the face, neck and trunk while the extremities are spared. This peculiar distribution of fat gives the patient the distinctive habitus sometimes known as the buffalo type of obesity. In patients with the adrenal cortical syndrome the same habitus may occur, although in my experience it occurs more frequently in persons with pituitary basophilism. Hirsutism and obesity may be comparatively slight in patients with adrenal cortical syndrome. Osteoporosis is common to both diseases. Pituitary basophilism is generally a slowly progressive disease, and by the time the patient consults the physician most of the characteristic symptoms and findings are present. As I have mentioned before, the adrenal cortical syndrome may appear with considerable rapidity, and in those cases in which the onset and progress of the disease are slow and the findings closely approximate those of pituitary basophilism, localizing evidence of an adrenal tumor is likely to be present. It is my impression from a study of the cases which have been reported and of those which I have seen that pituitary basophilism is more likely to occur in its classic form, whereas marked variations in the symptoms and signs of the adrenal cortical syndrome are encountered frequently.

It is possible that this variation in symptoms which occurs in cases of adrenal tumor may depend on the degree of maturity and differentiation of the cells which comprise the tumor.

Frank [80] has recently suggested a test for functional cortical adrenal tumors. In 1 case in which there was a large carcinoma of the adrenal cortex repeated examinations of the urine for hormones over a period of four weeks revealed that large amounts of the female sex hormones were secreted. Unverified cases of pituitary basophilism were similarly examined with negative results. It is to be hoped that further studies of this type will be made and that a differential diagnostic test can be developed. From what has been said it is obvious that there is a most urgent need for a method which will differentiate the various types of endocrine disorders capable of producing the syndrome. It is well to remember that in many cases

80. Frank, R. T.: A Suggested Test for Functional Cortical Adrenal Tumor, Proc. Soc. Exper. Biol. & Med. **31**:1204, 1934.

the cortical adrenal tumor is frightfully malignant. If surgical intervention is to have value in such cases it must be done early. The treatment of patients with pituitary basophilism at present is not particularly satisfactory. Roentgen therapy has in some instances resulted in retrogression of the symptoms. Much valuable time can be lost by prolonged courses of roentgen therapy to the pituitary body when the disease might have been cured by removal of an adrenal tumor. In many instances of adrenal tumor the distortion of the calices in the pyelogram will make the diagnosis, although it is important to remember that the absence of positive findings in the pyelogram does not necessarily preclude the existence of a cortical tumor.

Pathologic Physiology.—Experimental cortical hyperadrenalism has never been produced. In this respect the adrenal cortex appears to be unique in the endocrine system. Doses of the hormone which are greatly in excess of physiologic needs, when administered to normal or adrenalectomized animals, result in no untoward symptoms or metabolic changes. Attempts have been made by Simpson and his associates,[81] by Howard and Grollman [82] and by Kroc and Martin [83] to demonstrate an influence of potent cortical extracts on the sexual and other endocrine organs of animals. To my knowledge no such attempts have been made on human subjects. It is of some significance that Kincov, Zillessen and Rowntree [84] used enormous doses of the cortical hormone for a short time in the treatment of patients with Addison's disease. They were unable to observe any harmful effects or untoward symptoms. A consideration of the available evidence leads one to believe that it is highly improbable that the symptoms of the suprarenal cortical syndrome are the result of an excessive production of the substance now known as the cortical hormone. At this point it is difficult to refrain from asking the question: By what, then, are the symptoms caused if they are not the result of excessive amounts of the cortical hormone? Two answers immediately suggest themselves: (1) the presence of another hormone as yet undiscovered in the gland, and (2) the production of an abnormal hormone. According to Kendall, the latter possibility could

81. Simpson, S. L.; Kohn-Speyer, A., and Korenchevsky, V.: The Adrenal Cortex and Sex: Influence of Cortical Extract on Normal and Castrated Rats, Lancet **2**:1194 (Nov. 25) 1933.

82. Howard, Evelyn, and Grollman, Arthur: The Effect of Extracts of the Adrenal Cortex on Growth and Reproductive System of Normal Rats with Particular Reference to Intersexuality, Am. J. Physiol. **107**:480 (Feb.) 1934.

83. Kroc, R. L., and Martin, S. J.: The Relation of Bilateral Suprarenalectomy and Subsequent Extract Therapy on the Body Weight and Oestrual Cycle of the Albino Rat, Am. J. Physiol. **108**:438 (May) 1934.

84. Kincov, Jacob; Zillessen, F. O., and Rowntree, L. G.: Studies of the Adrenal Glands in Health and Disease: II. Effects of an Excess of Cortical Hormone in Addison's Disease, Endocrinology **18**:361 (May-June) 1934.

easily be true from the chemical point of view. This question, nevertheless, remains unanswered, and speculation is of no value except as it stimulates further investigation.

Surgical Treatment of the Adrenal Cortical Syndrome.—It is encouraging that more and more cases of successful removal of adrenal cortical tumors are being reported. Examples have been reported by Walters and his associates,[85] Collett,[58] Hicks,[68] Kolodny [69] and others. In the past the mortality following surgical intervention has been exceedingly high. This is partly because surgical technic had not developed to its present nicety and partly because in the presence of a tumor of one adrenal gland the other gland may be absent or atrophic. Even when normal the other gland apparently may temporarily cease to function after operation. Following surgical procedure it is advisable to observe the patient carefully for acute adrenal insufficiency, and if this develops to administer promptly the cortical hormone and saline solution.

HYPERFUNCTIONING MEDULLARY TUMORS

Hyperfunctioning tumors composed of primitive or adult medullary cells continue to excite medical and surgical interest. These tumors cause either continuous hypertension or attacks of paroxysmal hypertension probably as the result of an overproduction of epinephrine. The attacks are frequently associated with evidences of instability of the sympathetic nervous system, such as tachycardia, vasoconstriction followed by vasodilatation, emotional instability and other similar phenomena. C. H. Mayo [86] was the first to remove such a tumor successfully. Since then many similar cases have been reported, notably by Pincoffs and Shipley [87] and Porter and Porter.[88] The literature on this subject has recently been fully reviewed by Hick [89] and by Belt and Powell.[90] The last named authors summarized the data for 60 cases, reports of which had been published up to that time. Since then addi-

85. Walters, Waltman; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, Ann. Surg. **100**:670 (Oct.) 1934.

86. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve: Report of a Case, J. A. M. A. **89**:1047 (Sept. 24) 1927.

87. Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of the Suprarenal, Ann. Surg. **90**:742 (Oct.) 1929.

88. Porter, M. F., and Porter, M. F., Jr.: Report of a Case of Paroxysmal Hypertension Cured by Removal of an Adrenal Tumor, Surg., Gynec. & Obst. **50**:160 (Jan.) 1930.

89. Hick, F. K.: A Suprarenalin-Producing Pheochromocytoma of Suprarenal Gland, Arch. Path. **15**:665 (May) 1933.

90. Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla: Suprarenal Sympathetic Syndrome, Surg., Gynec. & Obst. **59**:9 (July) 1934.

tional cases have been reported by Eckardt,[91] Kalk,[92] Bauer and Leriche [93] and others. One case, in which the patient was a child of 14 years of age, was reported by Ernould and Picard.[94] In this case the tumor was malignant, and metastasis was found in the skull. Hypertension was present. The diagnosis of hyperfunctioning medullary adrenal tumor is often difficult. The blood pressure may be normal between paroxysms, and unless the patient is observed during an attack hypertension will not be noted. In cases in which the blood pressure remains continuously elevated the symptoms may not be sufficiently distinctive, and the patient may give the impression of having ordinary severe essential hypertension. Bauer and Leriche [95] emphasized the diagnostic importance of the parallel ascent of the curves of blood pressure and blood sugar.

OPERATION ON THE ADRENAL GLANDS

A discussion of the adrenal glands would be incomplete without calling attention to the work which has been done in the field of surgery for diseases not ordinarily considered the result of disturbances of the adrenal glands. Crile [96] has recently summarized the results of 350 operations which he performed on patients with such disorders. In 53 cases adrenalectomy was done and in 297 cases denervations. Beneficial results or cure was reported in cases of neurocirculatory asthenia uncomplicated by the presence of psychosis and in cases of peptic ulcer, recurring hyperthyroidism, diabetes, epilepsy and polyglandular syndromes. Results in cases of confirmed hypertension were disappointing. Crile based his surgical procedure on the theory that the human species pays the penalty for civilization by being subject to a group of kinetic diseases in which there is a continued or intermittent widespread stimulation of the neuroglandular system. The validity of his theory is yet to be confirmed.

91. Eckardt, Friedrich: Ueber Nebennierenmarkgeschwülste im Kindesalter, Monatschr. f. Kinderh. **61**:127 (Nov. 27) 1934.

92. Kalk, Heinz: Paroxysmale Hypertension, Blutdruckkrisen und Tumor des Nebennierenmarkes, Klin. Wchnschr. **13**:613 (April 28) 1934.

93. Bauer, Julius, and Leriche, René: Zur Klinik und Therapie des Paraganglions, adrenalogene Hochdruckkrisen, Wien. klin. Wchnschr. **47**:1224 (Oct. 12) 1934.

94. Ernould, H., and Picard, E.: Un cas de sympathome sympathogénique avec hypertension artérielle paroxystique, Rev. belge sc. méd. **6**:223, (March) 1934.

95. Bauer, Julius, and Leriche, René: Contribution clinique et thérapeutique à l'étude des paragangliomes et des crises d'hypertension adrénalinique, Presse méd. **42**:1385 (Sept. 5) 1934.

96. Crile, George: Pathologic Physiology of the Neuroglandular System, Am. J. M. Sc. **189**:276 (Feb.) 1935; Indications and Contra-Indications for Denervation of the Adrenal Gland, Ann. Surg. **100**:667 (Oct.) 1934.

Regardless of the theory underlying the procedure, the results are exceedingly interesting and warrant careful consideration.

DeCourcy and his associates [97] performed subtotal bilateral adrenalectomy for essential hypertension, which they designated as hypersuprarenalism. The basis for attacking the adrenal glands in cases of hypertension rests on the theory which has yet to be established that the cause of essential hypertension lies in the adrenal glands. DeCourcy's operation consists in the removal of about two thirds of the adrenal gland, in two stages. He gave the results in 6 cases, in 2 of which cortical tumors were present. It is impossible at present to evaluate DeCourcy's results. Further observation of these patients over an extended period is necessary.

It is interesting to note that attempts have been made to cure patients with Addison's disease by the transplantation of adrenal cortex. Beer and Oppenheimer [98] reported the results in 2 such cases. The first patient obtained some temporary improvement. The second patient obtained great improvement following transplantation, so that it was thought advisable to repeat the procedure several weeks later. The patient's condition improved so strikingly that the authors believed it justifiable to assume that the patient was suffering from Addison's disease and that the transplant "took." It seems likely that further developments in this field of surgery can be expected. The method developed by Stone and his collaborators [99] in transplanting thyroid and parathyroid glands might be applicable to the adrenal glands. According to this method, small fragments of the gland or a growing culture of the gland is transplanted after a period of growth in an artificial medium containing the body fluids of the host.

SUMMARY AND CONCLUSIONS

An attempt has been made to review the pertinent literature on the adrenal glands. Considerable difficulty was encountered in the selection of the material to be presented. The applicability of this material to clinical medicine was the criterion generally used in the selection which was made. Furthermore, much of the literature is not only controversial but difficult to evaluate. In such cases, I have attempted to approach the matter with an impartial and unbiased mind. If, unwittingly, my own personal feelings have crept in, I wish to apologize.

97. DeCourcy, J. L.; DeCourcy, Carroll, and Thuss, Otto: Subtotal, Bilateral Suprarenalectomy for Hypersuprarenalism (Essential Hypertension), J. A. M. A. **102**:1118 (April 7) 1934.

98. Beer, Edwin, and Oppenheimer, B. S.: Transplantation of the Adrenal Cortex for Addison's Disease, Ann. Surg. **100**:689 (Oct.) 1934.

99. Stone, H. B.; Owings, J. C., and Gey, G. O.: Transplantation of Living Grafts of Thyroid and Parathyroid Glands, Ann. Surg. **100**:613 (Oct.) 1934.

NOTE.—Since this article was submitted for publication, additional evidence showing the intimate relationship between sodium metabolism and the function of the adrenal cortex has been presented. Harrop and his associates [100] have been able to maintain the lives of adrenalectomized dogs over periods of five months solely by the administration of sodium chloride and sodium bicarbonate. These animals received no preparation of the adrenal glands. Both sodium chloride and sodium bicarbonate were necessary to maintain life. These investigators were led to try the combination of the two salts because of the observation that when sodium chloride alone was given to adrenalectomized animals sodium ions were lost from the body more rapidly than chlorine ions. This fact suggested the use of sodium salts other than sodium chloride. Allers and Kendall [101] have confirmed the observation of Harrop and his associates. They used two dogs which had been kept alive for several months by the administration of the cortical hormone. Administration of the hormone was discontinued, and the animals were placed on a diet containing sodium citrate and sodium chloride. To make certain that the intake of sodium chloride was distributed over the entire day, a 0.7 per cent solution of the sodium chloride was used as drinking water. This combination of sodium chloride and sodium citrate in the diet was continued for eighty-four days with one dog and one hundred and fifteen days with another. At the end of this time the animals were in excellent condition and had gained weight, and the chemical constituents of the blood were entirely normal. Both animals were extremely sensitive to withdrawal of either sodium chloride or sodium citrate.

It would appear from the experiments cited that in dogs, at least, the cortical hormone is not essential to life provided the electrolyte pattern of the blood is kept normal. Excellent reviews of the relationship of the metabolism of sodium to the adrenal cortex may be found in two articles recently published by Loeb and his associates.[102]

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100. Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, Margaret: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, J. Exper. Med. **61**:389 (June 1) 1935.

101. Allers, W. D.: The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, Proc. Staff Meet., Mayo Clin., to be published. Kendall, E. C., in discussion on Allers.

102. Loeb, R. F.; Atchley, D. W., and Stahl, Jules: The Rôle of Sodium in Adrenal Insufficiency, J. A. M. A. **104**:2149 (June 15) 1935. Loeb, R. F.: Glandular Physiology and Therapy: The Adrenal Cortex, ibid. **104**:2177 (June 15) 1935.

DISEASE OF THE THYROID GLAND

AN INTERPRETATIVE REVIEW OF PROGRESS TOWARD SOLUTION OF THE PROBLEM

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SURGICAL CONSIDERATIONS

Review of Progress in the Knowledge of Disease of the Thyroid.—Billroth in 1869 had performed partial thyroidectomy for goiter in 20 cases, with 8 deaths (40 per cent), and he stated: "To him who has had little practice in these operations it can easily happen that he removes the entire half of the gland instead of merely the tumor (enucleation) whereby the operation becomes very complicated and most dangerous." Most of the deaths were due to infection and only 1 to collapse (hemorrhage?).

The present review is concerned chiefly with those developments in surgical technic, clinical skill, therapeutic and preventive measures and scientific investigation which have greatly reduced the morbidity and the mortality in all types of disease of the thyroid.* As the most

* In this paper the term exophthalmic goiter has been used by preference except when the authors quoted made use of the designation Basedow's disease. In the older articles most authors included under these terms cases of adenomatous goiter with hyperthyroidism, which in turn included cases of so-called *Jod-Basedow*. In the more recent articles many authors have accepted the distinction, in accordance with the differentiation by Plummer, of adenomatous goiter with hyperthyroidism as a separate clinical entity apart from true exophthalmic goiter (true Basedow's disease). To distinguish between these two clinical conditions the continental writers usually follow the nomenclature of Aschoff, which is similar to that of Wegelin (school of Langerhans), and designate them, respectively, as struma adenomatosa basedowificata and struma diffusa parenchymatosa basedowiana (Basedow's disease). The unmodified term hyperthyroidism is used to include both the hyperthyroidism associated with adenomatous goiter and true exophthalmic goiter.

The terms endemic goiter and simple goiter are used by many writers as synonymous and include the colloid and adenomatous types (with or without degenerative changes). As endemic goiter in a considerable number of persons produces hyperthyroidism late in life (adenomatous goiter with hyperthyroidism), I prefer to use the adjective endemic instead of simple because the latter is often used to exclude hyperthyroidism, and although endemic goiter is not an ideal term its use should not be confusing. As will be seen from this review, the division of goiters into two great groups—endemic and exophthalmic—probably rests on a definite etiologic basis. However, in quoting other authors who may or may not agree with this implication I have used their own terminology.

striking recent advance has been in the reduction of mortality in exophthalmic goiter, I shall first trace the developments that have caused a progressive decrease in the surgical mortality in this disease to around 1 per cent in many large clinics where operation on the thyroid is extensively carried out and to even less than that figure in a few clinics.

That this result is not yet universal is indicated by the following reports: Labbé, one of the most noted of the French clinicians, in a special address in conjunction with Azerad to the French Surgical Society in January 1931,[181] stated that the surgical mortality rate among patients for whom he had recommended operation for true and typical Basedow's disease was greater than 25 per cent. Duval and Welti took exception to this figure as representative of French surgery, as did also Sauvé, who maintained that it was 5.1 per cent. In a reply Labbé [182] implied that diagnostic criteria would greatly influence the surgical mortality. At the German surgical congress in March 1931, under the chairmanship of von Schmieden, an entire afternoon was devoted to a discussion of the treatment of Basedow's disease. The special papers by Schneider,[306] Bürkle-de la Camp and others are notable for their frankness, and the authors [258] pointed out the necessity, as Labbé had done, of cooperation by the surgeons with the medical clinics and laboratories in order to reduce the mortality in the disease. The surgical review was presented by Sauerbruch, who, on the basis of observations on the cases of 430 patients operated on in the various German clinics, stated that the mortality rate varied between 8 and 48 per cent in the few years before the introduction of the Plummer method (*Plummerung,* as many German writers call it) of preoperative treatment with iodine, and that subsequent to its more or less general use the mortality rate had been reduced, on the basis of observations on 1,049 cases, to between 0 and 27 per cent. In Sweden, according to Engel, only 205 patients were operated on for the disease in Holmgren's clinic between 1913 and 1930, and 24.7 per cent of them died; although apparently not all these deaths were the immediate result of surgical procedure, the immediate surgical mortality must have been high, since following the introduction of the Plummer method it was reduced to 2.2 per cent in Troell's clinic and to 4.9 per cent in Petrén's clinic. In England the mortality, in general, was high, as was indicated by the statistics of Wallace and Wevill (1933) for the Edinburgh Royal Infirmary of 12.3 per cent in 285 cases during the preceding ten years; however, Romanis, in his last 900 cases, had a mortality of 2.5 per cent, but it is not clear when he began to use iodine. In Vienna, Starlinger and Brücke reported for the years 1911 to 1930 in von Eiselsberg's clinic that 290 patients with true Basedow's disease were operated on, with an immediate mortality of 7 per cent. In this country, the report of Maes and his collaborators (1934) indicates that the surgical mortality in cases of exophthalmic

goiter in a general hospital situated in a district where thyroid disease is comparatively rare may be high. Under such conditions, with several surgeons sharing the small number of cases, he reported 19 deaths in a series of 275 cases of goiter, probably only about half of which were of the exophthalmic type. This is a mortality rate, as he pointed out, from seven to fourteen times as high as was reported from clinics where the disease is not rare, where the individual surgeons have wide experience and where there is complete cooperation with the medical and laboratory services.

I shall attempt to trace as briefly as possible the development of knowledge which has led to the successful surgical treatment of exophthalmic goiter referred to in the second paragraph. It is a complicated but fascinating story and embraces many fields of endeavor.

Goiter, because of its prominence, must have been known and referred to in the oldest medical writings. According to Garrison, Actius of Amida, who lived in the era of Justinian I (527-560), wrote an interesting chapter on goiter. Roger of Palermo in his "Practica," which was written about 1170 and was the chief textbook at the School of Salerno, prescribed ashes of sponge and seaweed (rich in iodine) for the treatment of goiter or scrofula. Paracelsus (1493-1541) was the first to establish a correlation between cretinism and endemic goiter. The use of iodine, as such, in the treatment of goiter was first studied and recommended by Coindet in 1820. The syndrome now recognized as hyperthyroidism usually associated with exophthalmos was described by Parry in 1786, by Flajani in 1800, by Graves in 1835 and by von Basedow in 1840. The syndrome of hypothyroidism, myxedema, was first noted by Curling in 1850 and was more accurately described by Gull in 1873 and by Ord in 1878. Schiff in 1884 pointed out that in dogs the fatal result which followed complete thyroidectomy could be avoided by the previous transplantation of thyroid tissue. In 1890 Horsley, having produced artificial myxedema in monkeys (1884), proposed implantation of thyroid tissue as a method of treatment. Apparently Bettencourt and Serrano were the first to try the procedure on a patient, but only temporary benefit was obtained, probably, as they thought, owing to destruction and absorption of the implant. This led to the use of a glycerin extract of thyroid tissue by Murray in 1891, which he injected subcutaneously. In June 1892 Fox reported having given orally a thyroid extract, and MacKenzie, in July of the same year, reported the administration of fresh thyroid gland.

"The Operative Story of Goiter" up to 1883, which includes Mikulicz' major contribution in 1886, was fully described with complete references and quotations by Halsted [125] (1920) in his interesting monograph of this title. Halsted was chiefly concerned in tracing the development of surgical technic as exemplified in surgical procedure on

the thyroid gland, from the oldest known operation for goiter through Billroth's [347] preantiseptic and postantiseptic era, Kocher's early work and the proof by Mikulicz that partial thyroidectomy through the tissue of the gland is possible to the final bloodless technic developed to such a high level of excellency by Halsted himself.

Kocher of Bern performed his first operation on the thyroid in 1872, and in 1874 [163] he reported 13 thyroidectomies with 2 deaths. Complete removal of the thyroid gland was performed in 2 of these cases, and although 70 operations for goiter had been reported before 1850 and 146 up to 1877, these 2 extirpations of the thyroid gland reported by Kocher are probably the first successful operations of this type. He quoted Billroth as making the statement that it was not yet known whether or not a human being could survive the operation. Reverdin in 1882 made a preliminary report [294] of a peculiar condition following complete removal of the thyroid gland, which in the following year was more clearly described as cachexia strumipriva by Kocher (1882 and 1883) on the basis of 101 thyroidectomies with 13 deaths (12.8 per cent). Of these, 34 were complete thyroidectomies, with 3 deaths. Reverdin and Reverdin [295] in the same year gave a similar detailed description of the late effects produced by complete thyroidectomy in 22 cases. In some of Kocher's cases of cachexia strumipriva the condition was pure postoperative myxedema, while in others (as is now known) there was evidence of simultaneous parathyroid insufficiency (tetany). The correlation between the symptoms of thyroid insufficiency in cases of cachexia strumipriva and Gull's disease (myxedema) was pointed out by Semon in discussing a case presented before the Clinical Society of London on Nov. 23, 1883. As a result, a committee of the society was appointed, and presented its classic "Report on Myxedema" in 1888.[293] This should be read by every one interested in thyroid disease. Although Sandström had described the parathyroid glands in 1880, the tetanic group of symptoms sometimes occurring in cases of cachexia strumipriva and experimental thyroidectomy (which included parathyroidectomy) was unexplained until the physiologic importance of these symptoms was clarified by the studies of Gley in 1891 (references 101 to 104), Gley and Nicolas [106], and Vassale and Generali (references 331 to 333) in 1896. Halsted (references 120 to 122) and Halsted and Evans in subsequent reports added a great deal to the knowledge of practical methods of avoiding injury to the parathyroid glands as well as to a clearer understanding of their physiology.

Rehn [288] in 1880 performed the first thyroidectomy on a patient with Basedow's disease, and in 1883 he presented the patient before the Medical Society of Frankfort; the patient had remained completely cured during the three years following operation. In 1900 Rehn [289] was able to collect, by personal communication, records of thyroid-

ectomy on 177 patients with Basedow's disease from 37 different surgeons, with a mortality of 13.5 per cent; he collected reports of an additional 114 instances from the literature, in which there was a mortality rate of 11.4 per cent. He pointed out that if only the severe cases were considered (95) the mortality would be 22 per cent.

Following his extensive report on the results of complete thyroidectomy and recognition of the syndrome of cachexia strumipriva as myxedema, Kocher abandoned the operation of complete thyroidectomy and returned to the procedure of partial thyroidectomy, which was often simple enucleation of the goitrous tumor; in short order he reported successively the results of his first (1895),[167] second (1901)[168] and third (1906)[170] thousand operations. In Kocher's second thousand operations (in which were included operations for Basedow's disease, with a mortality of 8 per cent), the operative mortality was as follows: In 27 cases thyroidectomy was performed for the removal of a malignant thyroid gland, with 6 deaths; in 20, thyroidectomy was performed for strumitis, with 2 deaths; in 24, thyroidectomy was performed for morbus Basedow, with 2 deaths (8 per cent), and in 929, thyroidectomy was performed for simple goiter, with 4 deaths (0.4 per cent). In a total of 1,000 thyroidectomies of all types there were 14 deaths (1.4 per cent).

While several surgeons made early and important contributions to the development of the surgical treatment of exophthalmic goiter, during the next few years the major contributors in developing the field were Kocher in Europe and Halsted, C. H. Mayo and Crile in this country.

Albert Kocher[160] published in 1902 an exhaustive monograph of more than 300 pages on a complete analysis of the 59 cases of Basedow's disease (4 deaths) in which the patients had been operated on by his father. The beneficial results of operation were most gratifying: Seventy-six per cent of the patients were considered cured, 14 per cent were improved and 3.3 per cent were slightly improved; the mortality rate was 4.7 per cent. In the surgical treatment of Basedow's disease Kocher developed the principle of multiple operation, consisting of preliminary ligation followed by one or more partial thyroidectomies. Pages 197 to 199 are devoted to the discussion of the use of iodine, and it is obvious from this and from the histories of cases presented in the report that many of the patients received iodine before operation, with obvious temporary improvement, whereas others apparently were made worse by it (or became worse after its use). While microscopic examination of the thyroid glands revealed in most cases diffuse parenchymatous hypertrophy and hyperplasia, in some cases it did not, as one would anticipate in a district where goiter is endemic, and the patients in the latter group, as one today restudies these cases, were apparently

most harmed by iodine. One cannot help but regret that this distinction was not fully and completely recognized and also that these early investigators failed to distinguish the frequent sudden aggravation of symptoms in true Basedow's disease from the sudden omission of iodine from its actual beneficial effect while it was administered. In considering this and the later reports of Kocher and other surgeons who had a low mortality rate in their cases of exophthalmic goiter in contrast to the subsequent high mortality rate of from 8 to 48 per cent in the big European surgical clinics previously mentioned, compared with the recent low mortality rate reported from America after the demonstration by Plummer [281] in 1922 and 1923 of the value of iodine in the preoperative preparation and postoperative treatment of patients, it would be of interest to know whether or not iodine unknowingly played a rôle in some of the early surgical cases reported. Sauerbruch stated at the 1931 German Surgical Congress: "The astonishingly great difference in the number of deaths . . . cannot be attributed to variation in operative skill but must be attributed to the difference in the preoperative preparation." In light of this it would be interesting to know whether or not at the time of Kocher's lowest mortality rate iodine in some form or other was being extensively used in the University Hospital of Bern, either as medication or as an antiseptic, especially in view of the fact that Albert Kocher [162] in 1910 made an extensive study of the difference in the pathologic findings and the iodine content of glands with Basedow's disease, depending on previous iodine medication. Thompson, Brailey and Thompson [321] have shown that 1 drop of compound solution of iodine U. S. P. daily will in many cases be sufficient to lower the basal metabolic rate and in some instances prevent the fatal crisis of exophthalmic goiter. Even if no iodine was administered to the patient the "odor" of iodine, if it was being used extensively in the hospital and was continuously inhaled by the patient, might be sufficient to have an appreciable effect. Lerman and Means have shown that the inhalation of ethyl iodide is as efficacious as the ingestion of potassium iodide. Furthermore, Aschoff's pupil, Uffenorde, in beautifully conducted experiments has shown that the air at Bad Salzungen in Thuringia (the spray from the spring enriching the air with iodine) prevents the development of endemic goiter in rats which at Freiburg develops in rats under otherwise identical conditions. The following observation by Ochsner (1905) suggests that some comparable change in technic may have been made by others but without recognition of the significance:

> I have had a peculiar experience in regard to use of iodoform gauze in these cases. Some years ago Kocher made the statement that in thyroidectomy no antiseptic solution should be used. Before that time I had tamponed the raw surface with iodoform gauze—and the patients went on to recovery without any disturbance. Then when this statement was made I simply inserted a small drain

tube and used no iodoform gauze, but the patients did not do so well. That being the only difference in treatment, I went back to the use of iodoform gauze and my patients did better again.

In fact, an excellent example of the unsuspected effect of iodine was the experience of Halsted [116] in the production in dogs of compensatory hypertrophy of the remnant of thyroid tissue after nearly complete thyroidectomy, which was first observed by him in 1888 and commented on by Welch. Halsted did not report these experiments in detail until 1896; [117] in the second series he reported, in 1914,[124] he was disturbed because he was unable to duplicate the compensatory hypertrophy obtained in the first series. In some of the later operations iodine was used as a disinfectant of the skin although not in all instances; however, iodine was freely used about the laboratory, and the vapor was therefore prevalent. Consequently the presumption is, as was suggested by Marine in a letter to Halsted, that iodine was the cause of his conflicting results. Marine and Lenhart demonstrated as early as 1909 that iodine will prevent hyperplasia of the thyroid. It will be remembered by all those familiar with the details of the surgical technic that about this time iodine was extensively used as a wound disinfectant and that at the end of the operation the entire wound was frequently swabbed with a solution of iodine.

From this slight digression one returns to a consideration of the development of thyroid surgery. Kocher reported in 1906 his third thousand thyroidectomies for all types of goiter; there were only 7 deaths—a remarkably low mortality. Kocher's brilliant results naturally stimulated thyroid surgery throughout Europe, but no one was able to report such consistently low mortality rates, and only a few surgeons had the advantage of having a large amount of endemic goiter material on which to develop technic and experience. In this respect C. H. Mayo has been fortunate, in that Rochester, Minn., is situated in the center of the American goiter belt. Mayo reported early in 1904 [245] the cases of 110 patients who were operated on for goiter of all kinds, and by the latter part of that year [246] he had operated on 40 patients with exophthalmic goiter, with 6 deaths. Halsted [118] reported in 1905 that he had operated on 46 patients with mild symptoms of exophthalmic goiter, with only 1 death, and in 1907 [119] he reported 90 cases with only 2 deaths.* At the meeting of the Southern Surgical and Gynecological Society in December 1908 Mayo [247] reported 1,000 operations on 979 patients (of whom 574 had a simple goiter), with 4 deaths (0.7 per cent), and on 405 patients with severe hyperthyroidism, with 19 deaths (4.7 per cent); 4 of the last mentioned were among his first 16 patients.

* One wonders whether iodine could have played a rôle in Halsted's clinical results as it did in his experimental work just referred to. Also, in Baltimore, much sea food is eaten, which is rich in iodine.

Crile in 1908 [66] reported 225 operations on the thyroid gland; 142 of these were for benign tumor or hypertrophy with only 1 death, and 28 were on patients with exophthalmic goiter, with 4 deaths. These operations were performed prior to the introduction of his new technic of "stealing" the gland; in 13 cases there were no deaths after the introduction of that technic. This report of Crile's, together with his subsequent reports [67] on the advantages to be gained not only from "stealing" the gland, but also from his insistence on the careful handling of the tissues, as later embodied in his principle of "anoci-association," materially helped to reduce the operative mortality in exophthalmic goiter as well as in other fields of surgery.

The first really large series of patients operated on for hyperthyroidism was that reported by Mayo[248] in December 1910; he had then operated on 1,100 patients for hyperthyroidism, with the following mortality rates: following ligation, 3.7 per cent, and following thyroidectomy, 3.9 per cent.

In 1910 Kocher [172] reported 4,629 thyroidectomies for all types of thyroid disease. During this time he had performed 721 operations on 537 patients with Basedow's disease, with 17 deaths (3.2 per cent), of which 5 followed ligation. In his last 629 operations Kocher performed 462 on patients without symptoms of Basedow's disease, with no deaths, and 167 on patients with symptoms of Basedow's disease, with 4 deaths (2.3 per cent), although there were 5 additional deaths while patients were being prepared in the operating room, which, if considered due to the surgical procedure, would make the total mortality 5.4 per cent. The next year (1911 and 1912) he regrouped these and his additional cases on the basis of the number of operations, which gave a mortality rate of 2.3 per cent for 876 operations for Basedow's disease.

A consideration of the first phase in the development of the surgical treatment of exophthalmic goiter can be ended with the report of C. H. Mayo in 1914; during the twenty-six years ending July 1, 1914, he and his associates at the Mayo Clinic had performed 6,960 operations on the thyroid gland, of which 3,327 were for hyperthyroidism. The mortality rate in hyperthyroidism, on the basis of the number of operations, varied between 1 and 3 per cent, and as many as 278 consecutive operations had been performed without a death.

During this first phase many other contributions appeared which I am unable to include because of the limitation of space. Some of them contained reports of equally good results, although based on a much smaller number of cases; for example, an additional small series of 39 cases was reported by Halsted [123] in 1913, with no deaths. Although these papers contributed many important details to the general surgical

knowledge, they did not materially alter the general trend indicated by those specifically mentioned.

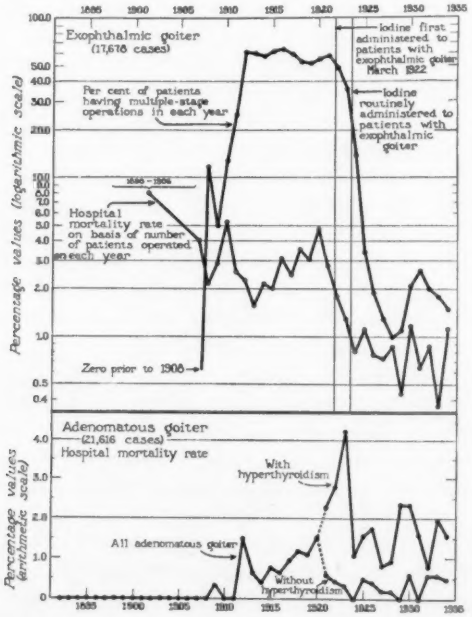
During the following ten years, between 1913 and 1923, which may be considered the second phase, the surgical treatment of exophthalmic goiter remained essentially stationary. In Europe the war stopped further progress, and even in this country it materially slowed down further developments with a few exceptions. Crile [68] continued to improve his technic of "stealing" the gland and developed his theory of the "kinetic drive." In 1922 [75] he reported a mortality of 1.4 per cent for his last 1,783 thyroidectomies, of which 1,022 were for exophthalmic goiter.

In the same year Pemberton [275] reported the following statistics for the Mayo Clinic from July 1, 1920, to June 30, 1921: One thousand nine hundred and fifty-four patients were operated on for goiter of all types (excluding cancer), with 35 deaths, giving a mortality of 1.8 per cent; 996 of these patients were operated on for simple goiter, with 8 deaths, making a mortality of 0.8 per cent; 281 were operated on for hyperfunctioning adenomatous goiter, with 4 deaths, making a mortality of 1.4 per cent, and 677 were operated on for exophthalmic goiter, with 23 deaths, making a mortality of 3.4 per cent, with a total of 1,234 operations, giving a mortality rate in cases of exophthalmic goiter of 1.9 per cent on the basis of the number of operations.

The third period of operation for exophthalmic goiter began in 1922. The preliminary report of Plummer, to the effect that the administration of iodine will prevent the crisis which causes death in exophthalmic goiter, was made at the meeting of the Association of American Physicians in May 1923. Under his direction iodine in the form of the compound solution (U. S. P.) was first administered early in March 1922 to patients with exophthalmic goiter in doses of 10 drops (0.6 cc.) three times a day as soon as they came under observation at the clinic, and the administration of iodine was continued until a considerable time after operation. The previous use of iodine and the reasons leading to Plummer's trial of it in a large series of cases will be discussed in a subsequent section of this review. I shall now merely present the evidence of its value in the treatment of patients with this disease by its effect "(1) in increasing the operability of the patient, (2) in decreasing the number of operations necessary, (3) in reducing or almost eliminating surgical mortality, (4) in decreasing and almost eliminating the medical mortality and shifting these formerly 'hopeless' into operable cases, (5) in almost completely transforming that group of postoperative patients who had some residual symptoms into complete cures, and (6) in completely controlling a large portion of recurrences."

Pemberton [276] and Pemberton and Haines [277] recently reported the surgical mortality in 27,057 cases of thyroid disease (excluding carcinoma) in which patients were operated on at the Mayo Clinic since 1918. In these papers they have given an illuminating discussion of the decrease in the mortality rate and of the increase in operability of exophthalmic goiter following the introduction of Plummer's method of the administration of iodine. Recently C. H. Mayo and Pemberton, under whose personal care a large proportion of the patients were, elaborated this study by including the cases of all patients operated on for goiter at the Mayo Clinic since the first operation for adenomatous goiter without hyperthyroidism, performed in 1892, and the first for exophthalmic goiter, performed in 1898, down to and including 1934. For the purposes of their study the records in the statistical department of the Mayo Clinic were checked and verified. Throughout the study a consistent method of recording deaths was adopted, as follows: All deaths were included which occurred in the hospital, irrespective of the duration of hospitalization, following any surgical procedure for either exophthalmic goiter or adenomatous goiter with or without hyperthyroidism, no matter what the immediate cause of death might have been (including 1 instance of suicide) and regardless of the severity of any complicating factor such as diabetes, organic cardiac disease, embolism or other complicating condition. Fifteen thousand, nine hundred and seventy-three patients were operated on for exophthalmic goiter and 21,255 for adenomatous goiter, making a total of 37,228 patients on whom 45,824 operations were performed; in addition, there were 442 patients with carcinoma of the thyroid, whose cases, however, will not be considered in this review. Beginning in 1918 the basal metabolism was determined by members of the section on clinical metabolism in many of the cases of thyroid disease, and since 1921 in practically all cases in which there was any question of hyperthyroidism; therefore, for the last seventeen years the clinician had these data to aid in making the correct differential diagnosis. With the exception of the very early years of the report, the members of the section of surgical pathology carried out histologic examination on all thyroid tissue removed, and the report was correlated with the clinical diagnosis at the end of each year by H. S. Plummer. Also, with the exception of the first few years, all the patients were seen and the condition was diagnosed in either the medical section of H. S. Plummer or that of W. A. Plummer by consultants thoroughly trained in making the correct differential diagnosis of thyroid disease. The data on the cases have been grouped according to the clinical diagnosis. Plummer's classification of goiter was used, and the cases were separated into two large groups: (1) exophthalmic goiter and (2) adenomatous goiter.

Space prevents an attempt to give the analysis of this immense amount of material by each year; therefore, I reproduce only the summarized tables in large yearly groups (tables 1 and 2 and a chart giving the yearly results). In the tables it will be noted that two subdivisions have been made on the basis of (1) the number of individual patients operated on each year (that is, a patient is counted once each year in which he or she was operated on, no matter how many operations were performed on him or her that year) and (2) the total number of opera-



Decrease in mortality with operation for goiter following introduction of the administration of iodine (C. H. Mayo and Pemberton, 1935).

tions performed (that is, the operation is considered as the unit). Every death in the hospital has been included, and the mortality rate has been expressed on the basis of these two subdivisions. Additional data are given in table 1 showing the percentage of patients in each yearly group who had more than one operation. All the data are presented in graphic form in the chart for each year, except for the cases of exophthalmic goiter before 1907, which have been presented as a group, as they were too few to give the yearly figures statistical significance. It is to be hoped that members of other clinics in which a sufficiently large number of patients are treated for thyroid disease will likewise present their data in

detail, as much of value about the disease as well as about the success or failure of variations in surgical technic and in the use of iodine could thereby be obtained which would justify the time and effort needed for its compilation.

In this review I shall refer only to the most important points brought out by this study. Following the use of iodine the mortality rate for patients with exophthalmic goiter, as is shown in table 1 and in more detail in the figure, was reduced to almost one fourth of what it had been before. Impressive as this is, it does not begin to tell the whole story, and the data presented must be considered in conjunction with another factor, namely, the increase in operability resulting from the use of iodine. By the administration of iodine the patient was in most instances rendered in a safe condition within from about ten days to three weeks or occasionally longer for

TABLE 1.—*Hospital Mortality Rate for Patients with Exophthalmic Goiter and Percentage of Multiple Operations Performed* *

Period	Hospital Mortality		Multiple Operations, Percentage of Patients
	Per 100 Patients	Per 100 Operations	
1898-1906	8.04	8.04	0
1907-1911	3.24	2.82	13.5
1912-1916	2.32	1.26	61.0
1917-1922	3.13	1.73	54.3
1923-1928	0.90	0.83	6.4
1929-1934	0.75	0.74	1.8

* From statistics correlated by C. H. Mayo and Pemberton (1935).

primary subtotal thyroidectomy, thus making almost entirely unnecessary the previous method of from one to four ligations followed in two to three months by subtotal thyroidectomy, even then not infrequently performed as a two-stage instead of a one-stage procedure. Not only was this a great economic saving to the patient, but it obviated completely the interim mortality—the rate of which was never exactly known, although it must have been appreciable. Likewise, the considerable number of patients who formerly came to the clinic in a cerebral or gastro-intestinal type of crisis for whom nothing could be done and who in consequence died shortly after arrival has been reduced to an insignificant figure as the result of immediate and adequate iodine therapy; nearly all these patients, as well as some others who, although they did not immediately die were too sick to be operated on, now in a few weeks become reasonably good operative risks, and it is in this group of formerly exceedingly sick patients that most of the small present-day mortality is found. The numerical importance of the increase

in operability is shown by the fact that in the eleven years before iodine was used approximately 58 per cent of the patients had multiple operations, such as ligation or the injection of hot water, and many of them had several such procedures before it was considered safe to attempt subtotal thyroidectomy, and subsequent to the use of iodine the number of patients who required multiple operations, including those for a recurrence of the disease, was reduced to an approximate average of 1.8 per cent for the last six years.

The mortality rate for patients with adenomatous goiter is given in table 2.

In the upper half of the chart is indicated the rapidity with which the necessity for multiple procedures was reduced by the use of iodine, together with the yearly surgical mortality rate in patients with exophthalmic goiter on the basis of the number of patients operated on and not

TABLE 2.—*Hospital Mortality Rate for Patients with Adenomatous Goiter* *

	Hospital Mortality					
	All Adenomatous Goiter		With Hyperthyroidism		Without Hyperthyroidism	
Period	Per 100 Patients	Per 100 Operations	Per 100 Patients	Per 100 Operations	Per 100 Patients	Per 100 Operations
1892-1906	0.00	0.00	....	....	....	....
1907-1911	0.13	0.13	....	....	....	....
1912-1916	0.71	0.70	....	....	....	....
1917-1920	1.22	1.21	....	....	....	....
1921-1928	0.87	0.86	1.70	1.67	0.34	0.34
1929-1934	1.03	1.03	1.96	1.96	0.32	0.31

* From statistics correlated by C. H. Mayo and Pemberton (1935).

on the number of operations done; in the lower half are presented similarly the data for patients with adenomatous goiter and, after 1921, with the hyperthyroid and the nonhyperthyroid forms, charted separately.

While iodine played the major part in the recent reduction of the mortality rate in surgical procedure in persons with exophthalmic goiter, other factors simultaneously have played a part in this reduction. First are the innumerable refinements in surgical technic which practically obviate injury to the recurrent laryngeal nerves and to the parathyroid glands (the dangers of hemorrhage were largely overcome in Kocher's time). In addition, if pneumonia develops postoperatively or the recurrent laryngeal nerve is injured, an occurrence which favors the development of pulmonary edema and pneumonia, the harmful effects of anoxemia can almost always be controlled by the administration of oxygen by means of the oxygen chamber or the modern oxygen tent, as demonstrated by Haines and me. Even if the parathyroid glands are injured the results are no longer feared, as the condition can be

easily and completely controlled by the proper use of calcium lactate, cod liver oil and parathyroid extract, the last being rarely needed (Boothby, Boothby, Haines and Pemberton and Boothby and Waltman).

Many patients who have had exophthalmic goiter, and especially those with adenomatous goiter with hyperthyroidism, for many years have a fatigued heart with more or less decompensation which is often superimposed on an independent organic heart disease such as valvular lesions, coronary sclerosis and angina pectoris. Medical cooperation in the handling of these cases before and following operation has been emphasized by many. The dangers of the improper use of digitalis were clearly brought out by Plummer, especially with the group of older patients who have adenomatous goiter with hyperthyroidism associated with decompensation. The proper care of the patient who has diabetes associated with hyperthyroidism has been particularly studied by Wilder and in Boston by Joslin and Lahey, and they have shown that the requirement for insulin is often greatly increased when the patient is on the verge of a crisis; the sugar content of the urine and the blood following operation must be carefully followed, and the appropriate amount of insulin must be used early to prevent the superimposition of diabetic coma. Wilder has shown that as the patient with exophthalmic goiter improves with iodine therapy there is corresponding improvement in the associated diabetes, with an increase in the carbohydrate tolerance and a reduction in the requirement for insulin (references 33, 34, 36, 37, 38, 40, 41 and 46).

Mention must be made of the use of iodine in the treatment of adenomatous goiter as opposed to its use in the treatment of exophthalmic goiter. At the Mayo Clinic iodine is not given except for special purposes to a patient who has adenomatous goiter without hyperthyroidism. However, since 1923 it has been freely given, but not as a routine, to patients who have adenomatous goiter with hyperthyroidism, and no harm has been noted from such use within the week or two before operation is performed. Some of the patients are better following its administration, and some have always shown periods of improvement without its use. The mortality rate shown in the chart in cases of adenomatous goiter with hyperthyroidism is possibly slightly lower after the use of iodine than before, but the decrease is not nearly so great as in cases of exophthalmic goiter. As a matter of expediency and safety iodine is usually given to patients with adenomatous goiter with hyperthyroidism to avoid the possibility of a fatal accident consequent to an erroneous preoperative clinical diagnosis which consists in mistaking a mild case of exophthalmic goiter with an incidental adenoma in the gland for a case of adenomatous goiter with hyperthyroidism.

Crile in 1928[69] and 1929[70] reported excellent surgical results in the treatment of hyperthyroidism, and in 1930[71] reported that he

and his associates had performed on Sept. 9, 1929, the twenty thousandth operation on the thyroid gland. Of such operations 5,354 were ligations and 13,814 were thyroidectomies; 10,125 of the thyroidectomies were for hyperthyroidism, 3,689 for simple goiter. Crile had one series of 982 operations without a death, if only patients less than 50 years of age are considered, and the mortality under his plan of management embraced in his principle of anoci-association, of stealing the gland and of multiple operation had been reduced to 0.5 per cent for all operations. During the last few years Crile (references 72 to 74) has been intensely interested in the rôle the adrenal glands may play in the syndrome of exophthalmic goiter, and his most recent reports have been concerned chiefly with that interesting phase of the problem of thyroid disease. The results he has already obtained are very interesting; they are, however, as yet inconclusive as to the clinical value of this method of attack.

Another wonderful record for American surgery is found in the results reported by Lahey [186] in 1934 (table 3). He adopted essentially

TABLE 3.—*Results in Treating Hyperthyroidism* *

	Cases	Operations	Deaths	Patients, Percentage of Mortality	Operations, Percentage of Mortality
Primary hyperthyroidism (Basedow's disease)...	3,422	4,543	21	0.61	0.48
Toxic adenoma.....	876	1,032	16	1.80	1.50
Total.....	4,298	5,575	37	0.86	0.66

* Based on results reported by Lahey (1934).

the classification used by Plummer, but he did not divide his statistics in such a manner that the effect of iodine can be determined, probably because comparatively few of his patients were operated on in the pre-iodine era.

In a five year follow-up in 97 cases Lahey [187] found 82 patients who were perfectly well, 7 who were well after another operation and 3 who were well, but only with the constant administration of iodine. In conjunction with Hurxthal, Lahey commented at length on the postoperative end-results in 300 patients with thyrocardiac disease.

In addition to the three large series of operations on the thyroid just detailed, many smaller series with similar good mortality rates could be cited from the American surgical literature. In fact, as a result of the general use of iodine before and after operation thyroid surgery is performed satisfactorily and with a low mortality rate in nearly all surgical clinics in the American goiter belt and wherever exophthalmic goiter is prevalent. Reports during the last year in Europe, a few of which I have previously referred to, are rapidly increasing in number and show a greatly decreased mortality

rate as the members of the various European surgical and medical clinics have adopted and have become familiar with the details of the correct method of administration of iodine in cases of exophthalmic goiter.

This section of the review can best be ended with mention of the contribution to the knowledge of thyroid surgery made in England by Joll.[148] In a series of 702 cases of exophthalmic goiter he had a mortality rate of 2.9 per cent; however, in the earlier part of his series apparently either iodine was not used or experience was being acquired in its use, which probably explains why the mortality rate was slightly higher than in some of the series recently reported on in this country.

Results of Medical Treatment.—No very accurate statistics on the medical treatment of exophthalmic goiter are available. In 1918 McCarrison[216] collected all the available data and concluded that with rest and ordinary medical attention it may be reasonably expected that at least 50 per cent of all patients will eventually recover to the extent of being capable of fulfilling their daily duties more or less efficiently. Thus, of 3,523 patients so treated whose cases he was able to find records of in the literature, recovery was stated to have occurred in just over 50 per cent; in 39 per cent the condition had been alleviated or had become chronic, whereas death had resulted from the disease itself in 12 per cent. In fatal cases death usually occurred within a period of from six months to six years after the onset; in more than 50 per cent it occurred within eighteen months.

The most recent statistics on the nonsurgical treatment of exophthalmic goiter are in the excellent study of Eason and Wallace (1932). They divided their cases into two groups: Group 1 (1921-1926) contained 180 patients. In the follow-up replies were received as to the condition of 143 patients; of these, 120 were known to be alive, and 23 were known to have died, which is a mortality of 16.1 per cent, if it is assumed that those not heard from were alive. Ten of those who died were definitely known to have died as the result of the exophthalmic goiter. Twenty of the patients reported that they were unfit for work.

Group 2 (1927-1930) contained 135 patients. In the follow-up replies were received as to the condition of 118, of whom 114 were known to be alive and 4 to have died, which is a mortality of 3.4 per cent, again if it is assumed that those not heard from were alive. Twenty-nine of those reporting said that they were unfit for work.

With the reduction of the surgical mortality to less than 1 per cent and with that mortality occurring in large part in the severe cases of long standing, interest in roentgen therapy as a means of controlling the syndrome of exophthalmic goiter has almost entirely disappeared.

Even if all the claims made by the advocates of roentgen therapy are granted, the results are so inferior to those obtained by partial thyroidectomy in conjunction with the proper use of iodine that space need not be taken here to present the facts in detail.

IODINE THERAPY

The changeable rôle that iodine has played in the treatment of various forms of goiter must now be traced. As has been mentioned, the ancients discovered that seaweed, which is now known to contain iodine, was beneficial in the treatment of goiter. Following the report of Coindet in 1820 of its beneficial effects iodine was used extensively, and the literature of the time contained many favorable as well as unfavorable reports. It became such a popular remedy that the people, according to St. Lager (1867), carried small bottles of iodine hung around the neck like a charm. From the work of Aschoff's pupil, Uffenorde, it is now known that this practice would probably be a reasonably good prophylactic procedure. Chatin [56] (1851-1854) carried out extensive investigations of the distribution of iodine in water, in the soil, in plants, in animals and even in the air; he concluded that a lack of iodine was the cause of goiter and recommended that in districts where goiter was endemic it could be prevented by adding iodine to the water supply. His proposal was not, however, accepted by the French Academy. Since his work no systematic investigation of the distribution of iodine in water and soil was made until the recent work of McClendon (1923-1934) and, to a lesser extent, that of von Fellenberg. Gley,[105] according to Garrison, in 1889 demonstrated the existence of iodine in the thyroid gland and blood. Although this attracted no attention, Kocher [166] (1895) suggested that the normal gland probably contains iodine. E. Baumann (1895 and 1896) definitely proved this fact and separated an iodine-containing compound from the thyroid gland which he called thyro-iodin and latter iodothyrin. Murray in 1891 and Fox and MacKenzie independently in 1892 had shown that thyroid extracts administered either subcutaneously or orally would control myxedema, and it was quickly demonstrated that iodothyrin produced the same clinical effect. Hutchison (1896 and 1898) investigated the proteins of the thyroid gland which were first described by Bubnow in 1884. Oswald [272] demonstrated (1896 to 1901) that an iodine-containing thyroglobulin could be satisfactorily purified from the proteins of the thyroid gland and that it was physiologically active and therapeutically effective in myxedema. He [273] demonstrated that the iodine content of the thyroglobulins obtained from persons with goiter was much lower than that of thyroglobulins obtained from the thyroid glands of animals; the iodine content was very low in the thyroglobulins obtained from persons

with exophthalmic goiter. It therefore became evident that the functional and pathologic activity of the thyroid gland is in some way connected with iodine. The rôle which iodine plays in the formation of the normal secretion of the thyroid gland was not finally cleared up until after Kendall in 1914 (1915; 1919) isolated thyroxine in crystalline form; Harington in 1926 (references 127 and 128) determined its structural formula and Harington and Barger synthesized it in 1927.

Although much was written in the older literature for and against the administration of iodine to persons who had simple goiter, no systematic study of the problem was made until Kocher [166] emphasized the harmful effects often produced by its uncontrolled use in the endemic goiter district of Switzerland. Under his direction an extensive clinical and chemical study was made of the problem by his son, Albert Kocher.[161] One of the best of Theodore Kocher's articles on the use of iodine in the treatment of thyroid disease was published in 1905 as a lecture on "Die Therapie des Kropfes" in *Deutsche Klinik*.[169] In this study he presented clearly the various types of goiter for which iodine can be given with safety and emphasized the harm that can result to patients with a certain type of goiter from an indiscriminate and unguided use of iodine. Kocher was very emphatic about the dangers of iodine, especially those from the injection of iodine directly into the thyroid gland. On the other hand, he remarked on the occasional brilliant results which he had observed as well as found reported in the literature following the administration of iodine to patients with Basedow's disease.

There seems to be no doubt that he saw many patients with simple endemic goiter [171] but who had no, or only slight, constitutional symptoms of hyperthyroidism and who became worse following the use (or possibly the misuse) of iodine. The syndrome thus produced resembled that produced by an overdose of preparations of thyroid gland, which in turn resembled that of Basedow's disease. For this condition Kocher [172] devised the name *Jod-Basedow*, although he recognized that it was not true Basedow's disease but a "frequent and important form of Basedow's disease which is brought about by the (improper) administration of iodine to patients with endemic goiter." In all his papers he so emphatically emphasized the dangers of the "improper" use of iodine that the members of the medical profession were led to believe that it was malpractice to give a patient with Basedow's disease iodine in any form, in spite of the reports of almost miraculous benefit which occasionally appeared in the medical literature and the cases which Kocher himself had observed. As emphasized by Means and Lerman in their paper on this subject which was read last May at the meeting of the American Medical Association, the choice of the name *Jod-*

Basedow was most unfortunate on account of the erroneous connotation therein implied that true Basedow's disease may also be caused by the administration of iodine. However, the intensive form of endemic goiter existing through, and producing its effect over, many generations, including a prenatal influence, does not occur in the United States. Therefore, in this country one must be guarded as to the judgment of the effect which iodine may produce in this type of goiter and in the various forms of cretinism which develop in such an environment.

According to Albert Kocher [160] (1902), the reports made by Langerhans on the pathologic changes in the thyroid gland showed in most cases diffuse parenchymatous hypertrophy, thus agreeing with Greenfield's (1893) and Lubarsch's [202] (1895) observations as to the characteristic pathologic changes in true Basedow's disease. However, as some cases of adenomatous goiter with hyperthyroidism (*Jod-Basedow*) are included in Kocher's series,[172] there were many instances in which the pathologic changes were those usually seen in cases of endemic goiter, thus confusing the clinicopathologic correlation of Basedow's disease.

In a pathologic and chemical study of 160 thyroid glands from patients with Basedow's disease, Albert Kocher [162] found in only a fifth of the glands a nodular type of goiter, whereas in four-fifths there was diffuse hypertrophy of about the same degree throughout the gland, although the intensity of hypertrophy varied in degree in different cases. He also found that the degree of hypertrophy varied with the iodine content, which in turn depended on how recently the patient had been receiving iodine.

MacCallum reported a high incidence of diffuse parenchymatous hypertrophy and hyperplasia in the thyroid glands removed by Halsted from patients with exophthalmic goiter. Wilson (1908; 1913; 1914; 1915; 1916; 1922) and MacCarty (1912; 1913; 1931) found a similar high ratio in thyroid glands removed at the Mayo Clinic when correlated with Plummer's peroperative diagnosis of exophthalmic goiter and adenomatous goiter with hyperthyroidism (at that time Plummer was noncommital in his terminology and used the terms toxic hyperplastic and toxic nonhyperplastic, respectively). On the other hand, Marine and Lenhart (1911) studied the thyroid glands removed at Lakeside Hospital (Crile's surgical and Hoover's medical service) and found no consistent pathologic changes in cases in which the diagnosis was exophthalmic goiter. However, they made one important observation: Of all the cases in which the clinical diagnosis was exophthalmic goiter, in those in which active hyperplasia was evident there was a higher mortality, namely, 25 per cent. It was this difference in the mortality rate which made all members of surgical clinics, at a time when the

field of thyroid surgery was being developed, loath to exclude from their statistics on surgical mortality the other groups of cases with a lower mortality rate in which the condition resembled but was distinguishable by accurate study from true exophthalmic goiter. This led to the more general use of the term hyperthyroidism which, although inclusive, readily admits subdivision into primary (exophthalmic goiter) and secondary (adenomatous goiter with hyperthyroidism) conditions. This distinction, when desirable, can be omitted in reports on mortality. (The present-day reversal in the mortality rate has obviated this objection whenever iodine is administered properly.)

Plummer,[280] as is well known, has consistently maintained that the two clinical syndromes of exophthalmic goiter, that associated with diffuse parenchymatous hypertrophy and hyperplasia of the thyroid gland and that of adenomatous goiter in which diffuse extra-adenomatous hyperplasia is absent, are distinct clinicopathologic entities. The best presentation of the pathologic anatomy of the thyroid gland in relation to variations in its activity is contained in Plummer's article on "Functions of the Normal and Abnormal Thyroid Gland" in "Oxford Medicine" (1922). The most extensive presentation of the reasons leading up to the use of iodine in the treatment of exophthalmic goiter, the method of its administration and the results from its use are given in the Beaumont Lecture delivered by Plummer[282] in the autumn of 1925.

It is impossible briefly and adequately to summarize these articles, and I can only bring out here two points which are necessary in my attempt to correlate the recent experimental work, initiated by Loeb, which has resulted in producing in animals a syndrome closely resembling the syndrome of exophthalmic goiter in man: 1. Endemic goiter appears to develop as the result of an increase in the normal stimuli of potential hypothyroidism (that is, a concentration of thyroxine in the tissues slightly below normal), which gives rise to normal stimulation of the thyroid gland to make up this deficiency which develops under conditions of an insufficient supply (concentration) of iodine. Endemic goiter can be prevented by the prophylactic administration of iodine, as was conclusively shown by Marine and others; McCarrison[216] has also emphasized that contributing factors, for example, filth, insufficient diet and so forth, should, if present, be remedied. The demonstrable pathologic changes in the thyroid gland under these conditions are, first, possibly transient hypertrophy and hyperplasia followed by deposition of colloid and the formation of new acini, thus producing adenomatous goiter without hyperthyroidism. Late in life this adenomatous goiter may deliver to the tissues an excess of thyroxine normal in character which produces the hyperthyroidism of adenomatous goiter; a sudden increase in the amount of thyroxine which the adenoma-

tous or surrounding tissues delivers to the body seems at times to be initiated by the administration of iodine (Kocher's *Jod-Basedow*[172]). 2. The ultimate cause of exophthalmic goiter is unknown, but evidence suggests the theory that the immediate cause is the sudden springing into activity of some unknown type of abnormal stimulation which forces the thyroid gland (which up to that time usually is normal) to make and deliver to the tissues an excessive secretion that is in part thyroxine and in part some abnormal intermediate by-product. It is the variation in the properties of these two products that makes up the variable syndrome of exophthalmic goiter before and after the administration of iodine and the abolishment of the abnormal product by iodine which is the most important factor in decreasing the mortality rate. Although Moebius in 1887 suggested that exophthalmic goiter is due to dysthyroidism, Plummer's two-product theory is in no way related to that idea. Confusion has arisen from the fact that if this unknown stimulus to the thyroid gland suddenly develops in a subject who has had a preexisting endemic goiter the histopathologic picture will be confusing. Of cases at the Mayo Clinic, in approximately 30 per cent in which exophthalmic goiter developed the thyroid gland had previously contained adenomatous tissue; the proportion of such cases would vary greatly in districts where endemic goiter was common from the proportion in those in which it was rare.

One of the best recent pathologic descriptions of the different forms of goiter is that of Aschoff, which was presented by him at the International Conference on Goiter in Bern in 1927. This paper should not only be read but studied. Throughout his article Aschoff repeatedly insisted on the sharp distinction between endemic goiter in its various forms and the thyroid gland in exophthalmic goiter. Unfortunately, I can give only the following brief excerpts:

> Basedow's disease is no real thyroxine poisoning, that is to say, no ordinary hyperthyroidism.
>
> Before we turn to this question and to that of the causation of goiter, we must still make brief mention of a form of struma, which really does not belong to our subject of Endemic Goiter. This is the so-called Basedow goiter, Graves' disease, or exophthalmic goiter, which makes its appearance everywhere in the world. It takes its origin independently of endemic goiter noxa. The transformations, which a Basedow thyroid gland makes manifest to us, are well enough known. It is here far less a question of a proliferation process of the thyroid tissue, as we see in the puberty swelling or even in the puberty struma, but of alterations of the follicular epithelium within the follicle. The epithelium becomes greatly enlarged, becomes almost high-cylindrical, presses forward papillary-like into the cavity of the follicle and there takes the place of the more or less disappearing colloid. In this manner the individual follicles take on the appearance of central caniculi with abnormally high epithelium. How far in the ordinary Basedow thyroid gland there is also a proper new formation of thyroid follicles

going on, must remain open in the individual case. However, this does not play so important a part. We also get here the impression that there is something wanting as regards maturity, but more in the functional than the morphological sense. The nature of the development reminds us of the parenchymatous strumas of the period of puberty, but is distinguished from it through the special prominence of the epithelial hypertrophy. Thus it happens that we can observe transition structures between the Basedow thyroid gland and the Struma parenchymatosa, although both differ greatly from each other in their outspoken forms.

In contrast to the thyroid of Graves' disease which shows marked symptoms of hyperthyroidism, in the case of the goitrous thyroid it is rather the picture of hypothyroidism with all stages down to complete cretinism. Only in a few cases does goiter exhibit hyperthyroidism. Such are usually late forms of the goiter of puberty or so-called toxic adenoma.

Marine,[224] however, in a paper read at the same meeting briefly stated that "adenomata were one of many morphological states that might occur in the thyroid in Graves' disease and their presence offers no basis for assuming Graves' disease and 'toxic adenoma' are different in any essential feature."

In the general discussion following the main papers on the pathologic anatomy of the thyroid gland Helly of St. Gall stated that when he was in Vienna he found the characteristic histologic picture in cases of Basedow's disease but did not find it so often in cases so diagnosed in St. Gall. On the other hand, de Josselin de Jong of The Netherlands said that in his country there was a characteristic histologic picture in the thyroid gland of patients with Basedow's disease; the Basedow struma has no real relation to the problem of endemic goiter. Lubarsch [203] of Berlin, who in 1895 was the second (Greenfield, in 1893, being the first) to outline the characteristic structure of the thyroid gland in cases of Basedow's disease, was emphatic in maintaining that the histologic picture of this disease is characteristic and of absolute diagnostic significance.

De Quervain [286] said:

> Endemic goiter is, so to say, the antagonist of the genuine Basedow. To be sure the latter occur in goitrous districts, but all the more seldom, the nearer we approach the endemic center. It accordingly is more rarely found in Bern than in Basel and affects there not more than 1 to 2 per cent of the cases of struma that are operated upon, if we consider only the native patient. . . . On the other hand, endemic struma gives us the great majority of iodine-Basedow cases. Whereas incredible quantities of iodine can be borne without any thyrotoxic disturbance by most individuals, who have normal thyroid glands, with goiter sufferers it frequently happens that daily doses of one-half to one milligram of iodine causes Jod-Basedow to develop which lasts for months if not even for years. . . . But it is also a fact that struma basedowificata produced by iodine affects only a small percentage of goiter sufferers who are taking iodine. . . .
>
> To look upon struma basedowificata or at least the toxic adenomas as a hyperthyreosis and upon genuine Basedow as a dysthyreosis (Plummer) facilitates the explanation of many clinical observations. . . .

Friederich von Mueller [260] said: "The different geographical distributions of genuine Basedow's disease from the localization of endemic goiter with secondary hyperthyroidism speaks decisively for a separate position for genuine Basedow's disease. . . . We immediately meet with a difficulty—how can we decide in any individual case whether a true Basedow or a secondary hyperthyroidism is present?"

This clinical differentiation is admittedly difficult, especially in those districts where the incidence of endemic goiter is high, because under these circumstances any one in whom exophthalmic goiter develops must have a high percentage of chance of already having had one of the various forms of endemic goiter. In between a fourth and a fifth of the patients at the Mayo Clinic for whom a diagnosis of exophthalmic goiter is made there is more or less adenomatous hyperplasia, which produces a nodular goiter; the pathologic report in these cases is "adenomas in a hypertrophic parenchymatous thyroid." It is, of course, in this group that the most frequent errors in the clinical differential diagnosis occur, and in districts like Switzerland where the goiter is endemic the correct differential diagnosis in individual cases would be even more difficult. Means (1935) says that in Boston (where endemic goiter is exceedingly rare) he is not certain that there is any difference in the two diseases.

It seems obvious from a review of the literature that the pathologists have had difficulty in correlating a characteristic pathologic picture in cases of exophthalmic goiter in those clinics only where no serious attempt was made by the clinicians to make an accurate and careful differential clinical diagnosis or where one of the two diseases was disproportionately rare. It has been interesting to watch Fellows of the Mayo Foundation during their period in Plummer's goiter service attempt to make a differential diagnosis between exophthalmic goiter and adenomatous goiter with hyperthyroidism, and also to watch them separate the neuroses which simulate these syndromes. When first on the service they were usually wrong a little more than half the time; at the end of a year their preoperative diagnosis checked with the histologic reports of the section of surgical pathology in from 60 to 80 per cent of the cases. The consultant's preoperative diagnosis checked with these pathologic reports in better than 85 per cent of cases, and only the senior consultants obtained an agreement of 90 per cent or better. For twenty-five years H. S. Plummer has restudied at the end of each year all the clinical histories in which there was disagreement between the clinical diagnosis of exophthalmic goiter and the report of the pathologist as to the presence or absence of characteristic diffuse parenchymatous hypertrophy and hyperplasia. These discrepancies together with an analysis of the patient's symptoms were then discussed and studied with

his associates, and as a result there has developed a high degree of accuracy in the differential diagnosis. The opportunity of repeating such a study in this country has nearly passed because of the fact that endemic goiter is rapidly disappearing and also because the general use of iodine in the treatment of exophthalmic goiter has decreased the average intensity of the diffuse hypertrophy as well as the severity of the symptoms characteristic of the disease.

Definite advance could probably be made in the clinicopathologic correlation of thyroid disease if the surgical pathologist would institute investigation of the cytology of the thyroid gland by studying the Golgi apparatus* in the thyroid cells along the lines of the work initiated by Okkels and Marie Krogh. I shall later refer to the significance of their results but only mention here that they have demonstrated a probable, although rough, correlation between changes in the Golgi apparatus and the activity of the thyroid cells as measured by the heat production. They found the Golgi apparatus distinctly hypertrophied in exophthalmic goiter. Okkels has presented evidence to show that apparently the mitochondria, the significance of which in exophthalmic goiter has been extensively studied by Goetsch, are responsible for the original formation of the secretions, whereas the Golgi apparatus is apparently involved in the ultimate discharge.

It was Plummer's insistence on the separation of hyperthyroidism into the two syndromes which was the crucial factor in enabling him to demonstrate the fact that iodine will practically eliminate the combined medical and surgical mortality in cases of exophthalmic goiter, as shown in the previous section of this report.

Plummer was by no means the first to use or describe the beneficial effect of iodine in the treatment of exophthalmic goiter. The classic accident related by Trousseau in 1867, when by mistake he wrote a prescription for tincture of iodine instead of for tincture of digitalis, is probably the first accurate description of the effect of iodine in this disease. Cheadle (1869 and 1875), Kocher [163] (1874), Marine [223] (1907), and, in later work which will be referred to subsequently, Waller (1914), Neisser (1920), Loewy and Zondek (1921) and probably others presented or referred to more or less extensive trials of iodine, but they were always prevented from proving the point by the fear of *Jod-Basedow* and the erroneous implication and hypothesis the name implied. Of course these futile attempts were known to Plummer [281] as well as to all acquainted with the literature.

* The Golgi apparatus consists of peculiarly staining droplets suspended in the cytoplasm of the cells, probably indicative of chemical reactions taking place at those points. In secretory types of cells, changes in size and position of these bodies can be correlated with the secretory function, and therefore they have a broad biologic significance for the histologist.

In March 1922 Plummer [281] decided that iodine should have an extensive trial under his supervision at the Mayo Clinic. The beneficial results were immediately apparent, and the first preliminary report was made by him [281] in May 1923 at the meeting of the Association of American Physicians. The first extensive report was by Plummer and me at the meeting of the Tri-State Medical Association in October 1923. Our report was based on observations on 400 cases, and it showed a definite decrease in the basal metabolic rate accompanied by a marked improvement in the general condition of the patient. Subsequent reports from the clinic confirmed the beneficial effect of iodine in the treatment of exophthalmic goiter, and it was established that 10 minims of compound solution of iodine (liquor iodii compositus) three times a day (a total of 2 cc. daily, containing approximately 25 mg. of iodine) was the best average dose which would abolish the characteristic intense nervous phenomena of the disease; usually lower somewhat the basal metabolic rate; decrease the pulse rate and the abnormally forceful heart action, thus slowing the abnormally increased circulation rate; abolish the capillary pulse; avert or bring the patient out of a gastro-intestinal or cerebral crisis and, finally, decrease the medical and surgical mortality rate. Although for a time iodine was used intermittently, it was soon found that such a procedure was bad, and that subsequently the patient apparently did not always respond as completely as at first. With the aforementioned dose it was found that major improvement began on the sixth or seventh day and reached the maximum on about the fourteenth day, at which time it was usually safe to operate (iodine therapy being continued without interruption); emaciated patients, however, with marked secondary organic degeneration of the liver or other organs became better surgical risks if allowed several weeks of recuperation, with a gain in weight. If for special purposes the administration of iodine was discontinued, no change was usually noted in the patient's condition for from four to six days, and then he gradually, although sometimes rapidly, became worse: The nervous phenomena returned; the basal metabolic rate rose, and the heart and circulation rates increased. This delay in reaction of from one to ten days was at first confusing, and it has served to confuse other observers and has caused misinterpretation of the effect of iodine, especially if administered alternately every ten days or two weeks. Considerable evidence accumulated that the intermittent administration of iodine is, to say the least, a technically bad and possibly even harmful procedure. No evidence was obtained to indicate that the disease was cured in the sense that the underlying cause was abolished. In fact, all evidence pointed to the fact that only the severity of the symptoms was decreased and death in the crisis prevented. In some of the cases, especially in those

in the milder or earlier stage, this decrease in severity of symptoms was equivalent to their complete abolishment; the symptoms, however, returned on cessation of iodine therapy unless the administration was maintained so long that it could be assumed that the unknown cause of the disease had spontaneously ceased to exist, as was known to occur occasionally.

To date more than 9,000 patients with true exophthalmic goiter have received as a routine at the Mayo Clinic, with relatively few exceptions for purposes of study, 10 drops of a compound solution of iodine three times a day (25 mg. of iodine) as a preoperative and postoperative procedure. Plummer reported that neither he nor his associates have seen a single case in which the reaction of the patient could be interpreted as indicating that this was too large a dose as far as the syndrome of exophthalmic goiter was concerned, although extraneous effects, like a cutaneous rash, occasionally developed. Means [253] (1935) also was emphatic in his statement that he had never seen the slightest harm from the use of iodine in the treatment of exophthalmic goiter and discussed at length so-called iodine-resistant cases. In the first few years that iodine was used Plummer found that the accidental omission of the regular dose just before operation might eventuate in a postoperative crisis. One or two deaths occurred in 1922 which could be directly attributed to this omission, and in consequence the routine technic was tightened up to prevent such an occurrence. At Rochester the concern has been not with the minimal amount which would produce a detectable or measured effect in selected cases but the minimal amount which would give the greatest protection against postoperative crisis and death to the largest number of patients.

The first to confirm these results by accurate studies was the group at the Massachusetts General Hospital where Means and Richardson organized a "thyroid clinic" for the purpose of studying the proper treatment of exophthalmic goiter. Starr, Segall, Walcott and Means in 1924 reported their conclusions as follows: 1. Iodine by mouth will produce abrupt remission in most cases of exophthalmic goiter. 2. The remission is often as rapid and as extensive as that following subtotal thyroidectomy. 3. It is beyond question that iodine is the causal agent of this remission. 4. Iodine alone as now used has not been shown to be sufficient to suppress the disease permanently. 5. After a patient with exophthalmic goiter has been taking iodine a rapid rise of the basal metabolic rate and an increase of toxic symptoms occurs within from one to two weeks if it is discontinued. 6. In some cases of exophthalmic goiter iodine has no observable effect.

At the Massachusetts General Hospital Means and his associates continued the careful study just referred to and determined the minimal

amount of iodine which would produce in a few selected cases a decrease in the basal metabolic rate and in the associated phenomena of exophthalmic goiter. Thompson, Brailey, Thompson and Thorpe (1930) showed that in some cases as little as 1 minim of compound solution of iodine a day decreased the basal metabolic rate and that around this minimal dose there was more or less correspondence in the effect of iodine on the basal metabolic rate, depending on the amount used.

With regard to the minimal dose, Plummer has emphasized that the immunity of a patient with exophthalmic goiter from a postoperative crisis does not necessarily parallel the decrease in the basal metabolic rate, nor does the minimal dose which produces the former necessarily accomplish the latter; these are two distinct effects of iodine, and confusion has resulted from considering them synonymous. This point has recently been emphasized by Thompson, Taylor and Meyer (1934), who now recommend the routine use of 10 drops of compound solution of iodine three times a day to avoid fatal accidents.

Lerman and Means (1931) studied quantitatively the effect of iodine in various forms and found no demonstrable difference between iodine as a compound solution and as potassium iodide; they also demonstrated that the daily inhalation of from 2 to 4 Gm. of ethyl iodide (much, of course, being wasted or lost) was equivalent to the daily consumption of from 0.2 to 0.4 Gm. of potassium iodide. Means [251] (1933) in an excellent paper on the use of iodine emphasized especially its diagnostic value, as pointed out by Plummer, in the differential diagnosis of the milder cases of thyrotoxicosis from neurotic conditions. In the former a decrease in the basal metabolic rate with a general clinical improvement usually occurs, while no change is recognized in the latter. Other recent important reports on the value of iodine in the treatment of exophthalmic goiter are those by Jordi (1932); Winkenwerder and McEachern (1932); Schneider and Widmann [309] (1933); Klose [157] (1933), who reported the important papers of the Second International Goiter Congress in Bern; Nell (1933); Breitner (1933); Gardiner-Hill (1933); Müller and Livadas (1933); Ewald (1933); Dennig and Schuelke (1934); Klose (1934; references 158 and 159); Tillgren and Sundgren (1934); Irsigler (1934); Schneider [307] (1934), and Dautrebande.

At this point special attention must be given to the use of di-iodotyrosine in controlling the peculiar symptoms and crisis of exophthalmic goiter. Harington and Randall in 1929 isolated 3:5 di-iodotyrosine from the thyroid gland and demonstrated that practically all the iodine in the thyroid which is not thyroxine is di-iodotyrosine. Naturally the interest in the physiologic activity of this substance was increased. Drechsel (1895) isolated an iodine-containing amino-acid

from coral (Gorgonia cavallina) which he named iodogorganic acid. This was proved in 1905 by Wheeler and Jamieson and in 1907 by Henze to be 3:5 di-iodotyrosine. No one had ever noted that di-iodotyrosine had any specific physiologic activity, yet because of its isolation from the thyroid gland and the fact, as Canzanelli, Harington and Randall (1929) pointed out, that it was probably the precursor of thyroxine in the synthesis of the latter by the body, its properties were properly reinvestigated.

Abelin (1931; references 1 and 2) presented evidence that tended to show that di-iodotyrosine decreases the heat production of rats fed thyroid substance, which led him to suggest that there is a normal physiologic inverse correlation between di-iodotyrosine and thyroxine. In 1933 he [9] presented additional evidence to the effect by showing a favorable effect on the decrease of heat production following the administration of thyroxine to thyroidectomized animals. Gutman, Sloan, Gutman and Palmer (1933) prepared 30 patients for thyroidectomy by the administration of di-iodotyrosine and found it to be just as efficient as any other preparation of iodine but no more so; they concluded that it has no specific effect, as suggested by Abelin. Canzanelli and Rapport (1933) compared the calorigenic effect of di-iodotyrosine and found that while it was seven times as effective as tyrosine it caused only 4 per cent of the calorigenic effect produced by thyroxine in dogs. Means, Lerman and Salter found no calorigenic action of di-iodotyrosine in myxedematous patients. Thompson, Alper, Thompson and Dickie (1934) demonstrated that in 2 patients with myxedema 3.7 Gm. of di-iodotyrosine administered in nineteen intravenous doses over a period of three weeks caused no clinical or metabolic change; a similar experiment with 5.1 Gm. in fifteen days also caused no change; in 1935 Thompson and his associates [326] possibly obtained a slight effect from 8.6 Gm. given intravenously in sixteen doses. Elmer [87] (1934) showed that di-iodotyrosine prevents hyperfunction of the thyroid gland of guinea-pigs following the administration of the thyrotropic hormone in the same degree as potassium iodide, and hence acts only in proportion to its iodine content; Delcourt-Bernard (1933) and Foster (1934) likewise found no difference between the action of di-iodotyrosine and that of other forms of iodine. At the symposium on thyroid diseases of the Royal Society (1933) in which Harington [128] and others took part no definite proof of the specific advantages of di-iodotyrosine was presented by Harington, although he stated that he favored its use in cases of exophthalmic goiter instead of iodine.

Until further and conclusive evidence is advanced of the supposed specific antithyroxine action of di-iodotyrosine, as well as its possible calorigenic action as found recently by Thompson, there is, to say the

least, no point in using it in preference to the more common and much cheaper preparations of iodine in the routine preoperative and postoperative treatment of exophthalmic goiter. It cannot be used as a substitute for desiccated thyroid or thyroxine in the treatment of myxedema, so far as present evidence indicates.

CALORIGENIC ACTION OF THYROXINE AND ALLIED PRODUCTS

That the fundamental and characteristic symptoms of hyperthyroidism are those of greatly increased metabolism was first recognized by Friedrich Müller in 1893.[259] He noted that patients with exophthalmic goiter lost weight rapidly and that a negative nitrogen balance developed in patients on a diet containing sufficient calories to maintain weight and nitrogen equilibrium in patients with other diseases. Magnus-Levy in 1895 introduced into the clinic the scientific method of measuring the respiratory metabolism and thereby the heat production, which had been developed in the physiologic laboratories of Lavoisier, Zuntz, Rubner and Voit. Magnus-Levy thus confirmed Müller's discovery of an increased metabolism in persons with exophthalmic goiter, and in addition showed a decreased metabolism in hypothyroidism or myxedema; in 1904 he reported a five month study of the effect of various thyroid preparations and of iodine on the heat production of a myxedematous cretin. He noted and recorded the slow relapse which took from four to six weeks after thyroid medication was stopped before the heat production regained its original low level, but he was not at that time concerned with the character of the "decay curve" of which he recorded three examples.

Although Rubner in 1883 had enunciated the law that the heat production of man and of animals was proportional to the surface area, the surface area formula of Meeh ($KW^{2/3}$) was not sufficiently exact for accurate clinical work on human subjects. Therefore clinical calorimetry did not come into use as a routine procedure in the study of thyroid diseases until after DuBois and DuBois (1915; 1916) developed a more accurate height-weight formula, and Eugene DuBois and his associates at the Russell Sage Institute, utilizing in part calorimetric studies of their own but in large part the exact determinations of Benedict of the Carnegie Nutrition Laboratory of Boston, published their standards for age and sex in 1915. Following the establishment of the DuBois or, as he prefers to have them called, the Russell Sage, standards, Means at the Massachusetts General Hospital and I, first at the Peter Bent Brigham Hospital in Boston and shortly after at the Mayo Clinic (1917), stimulated the rapid development of clinical calorimetry.

One can pass over the large number of studies which then appeared first to prove the practical value of the basal metabolic rate in the

correct differential diagnosis of thyroid diseases among themselves and in sharply differentiating from them the conditions which merely simulated in a confusing way either the overactivity or the underactivity of the thyroid gland.

As I have stated, Friedrich Müller [259] first showed that the metabolism in cases of exophthalmic goiter was increased by the finding of a negative nitrogen balance and loss of weight of patients on a diet sufficiently large both to maintain nitrogen equilibrium and to prevent loss of weight of patients with other diseases. From this observation it was concluded that a negative nitrogen balance is characteristic of the disease; that this is not true except in the stage of crisis was shown by Sandiford and me [42] in a preliminary report in 1921 and in more complete reports in 1923 [43] and 1924.[35] By means of carefully controlled experiments we showed that the nitrogen balance can be readily maintained if the dietary intake is sufficiently large to meet the requirements. To accomplish this it is necessary to give approximately twice the diet which would be sufficient to cover the basal heat production; the protein content should be from 1.5 to 3 Gm. per kilogram of body weight. This large intake of food in the older literature was often referred to as "bulimia" and was thought to be of a neurogenic nature. Sandiford and I have shown that such a large excess of food is necessary to maintain caloric and nitrogen equilibrium because of the presence of the following factors: (1) increase in basal heat production from 25 to 100 per cent above normal; (2) increase in restlessness and purposeless movements, although the patient is in bed, and (3) increase in the cost of performing work. Plummer and I had shown, by having patients walk on a treadmill with accurate measurement of the consumption of oxygen at rest and while walking, that patients with exophthalmic goiter and adenomatous goiter with hyperthyroidism are hardly more than half as efficient in their muscular movements as are normal persons. Since that report this interesting fact has been confirmed repeatedly.

Kendall (1915; 1916; 1917; 1919) isolated thyroxine in pure crystalline form in December 1914. He, in conjunction with Plummer, shortly proved in experiments on cretins and completely myxedematous patients that thyroxine is the active principle of the thyroid gland and that when administered in proper amounts it will restore such patients to a completely normal condition. In 1916 [278] and 1917 [279] Plummer noted that 10 mg. of thyroxine raised the heat production of a completely myxedematous patient weighing 70 Kg. to a normal level, and that the return to the original low level required a month or six weeks. Plummer concluded, therefore, that the normal amount of thyroxine in the body is somewhat less than 10 mg., or in the ratio of 1:7,000,000, and

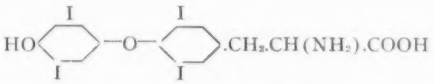
he pointed out that to produce such an immense amount of extra heat thyroxine must act in a manner similar to that of a catalyst. He also found that somewhat less than 0.5 mg. of thyroxine daily maintains the heat production at the normal level, and he therefore concluded that the amount of thyroxine made and discharged by the thyroid gland is somewhat less than this amount. As a result Plummer and, somewhat later, Means,[250] recommended that myxedematous patients and cretins be given daily the amount of thyroxine, as desiccated thyroid standardized on the basis of its content of organic iodine, which would just maintain the normal level of heat production. They found that on the average 2 grains (0.13 Gm.) of desiccated thyroid standardized on the basis of its organic iodine content, as recommended by the United States Pharmacopeia, is the correct daily dose for the large majority of such patients.

Reid Hunt (1923), by means of his acetonitrite test, shortly discovered that desiccated thyroid produced an effect greater than the equivalent amount of thyroxine (as iodine) in protecting mice against cyanide poisoning. Some of his experiments were based on the comparison between the effect of thyroxine and desiccated thyroid when both were given orally. Thyroxine is highly insoluble, which caused part of the discrepancy; however, the discrepancy persisted in the experiments in which the effect of an oral dose of desiccated thyroid was compared to that of a subcutaneous injection of thyroxine of equivalent iodine value. This discrepancy in the calorigenic action of thyroxine and of desiccated thyroid will be considered in greater detail later.

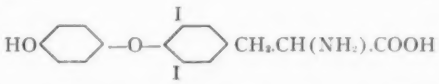
Sandiford and I with our associates (1925; 1926) carried out a balanced experiment on a completely myxedematous patient on a known diet and determined among other things the daily amount of thyroxine needed to maintain the heat production at a given level and also the peculiar characteristics of the decay curve. This part of the results was presented by Baldes and me at the Eleventh International Physiologic Congress. We were able to show that the amount of thyroxine in the body was approximately 7 mg. and that the daily amount of thyroxine needed to maintain normal heat production was 0.25 mg., both figures being slightly less than Plummer's first approximation. We demonstrated that 1 mg. of thyroxine produced by its elevation over the previous level of heat production in a completely myxedematous patient the equivalent of 1,000 large calories. We analyzed the decay curves obtained in this case and those obtained by Magnus-Levy referred to before and found that they were exponential, in our case the rate being 6 per cent per day and in Magnus-Levy's, 4 per cent per day. We showed that this exponential type of curve is consistent with the hypothesis that the extra heat production is proportional to the concentration of thyroxine in the body and consistent with the assumption that thyroxine acts as a catalyst in a monomolecular type of reaction.

Harington and Barger in 1927 synthesized 3:5:3′:5′-tetra-iodothyronine, which has been proved to be indistinguishable by chemical or physiologic tests from thyroxine, and, in conjunction with Anderson, Harington and Lyon immediately demonstrated that the synthetic product, when given intravenously to myxedematous patients, produced exactly the same clinical as well as calorigenic effects as the natural thyroxine. Its physiologic activity has since been confirmed by many observers.

Harington [129] established the structural formula of thyroxine as follows:



The last step in the synthesis of thyroxine is 3:5-di-iodothyronine, which has the following structural formula, with two less iodine atoms than thyroxine:



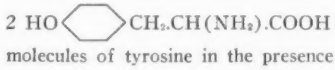
This compound, which Harington stated was easily synthesized, has been shown by Anderson, Harington and Lyon (1933) to be capable of raising the heat production of myxedematous patients in doses approximately fifty to seventy-five times as large as those of thyroxine. If further clinical experience substantiates this preliminary report and in addition demonstrates that di-iodothyronine will completely restore a myxedematous patient to a normal condition there may soon be available a very convenient preparation for therapeutic use in cases of thyroid insufficiency. Demonstration of its calorigenic effect, however, is not sufficient, because di-nitrophenol has a marked calorigenic action and yet cannot be used as a substitute for thyroxine.

The formula for 3:5 di-iodotyrosine is:

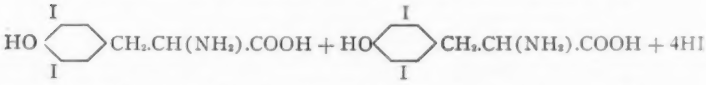
This is considered by Harington to be the probable intermediate stage in the biologic synthesis of thyroxine from tyrosine. He has shown that practically all the iodine in the thyroid gland which is not present as thyroxine is in the form of di-iodotyrosine. As I have pointed out, this substance has no (or possibly only a slight) calorigenic action on the myxedematous patient. Harington has pictured the synthesis in the body as a condensation of two tyrosine molecules in the presence of excess iodine, with the liberation of the aminoproprionic acid (alanine)

radical as a by-product either as such or as unknown degradation products. The starting point in the synthesis of thyroxine is the simple amino-acid tyrosine, which has the following structural formula:

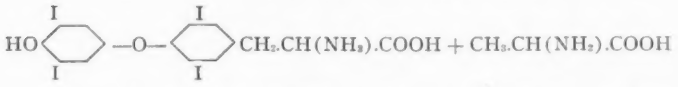
The synthesis of thyroxine then proceeds in the presence of excess iodine as follows:



two molecules of tyrosine in the presence of excess iodine form



two molecules of di-iodotyrosine which normally conjugate to form



one molecule of 3:5:3′:5′ tetra-iodothyronine (thyroxine) and the degradation products of the unused alanine radical.

Plummer [282] has suggested that the peculiar supplementary symptoms in exophthalmic goiter, which are not present in cases of adenomatous goiter with hyperthyroidism, may be due to the fact that in the synthesis of thyroxine, in the presence of an inadequate concentration of iodine and with the thyroid gland delivering an excessive amount of secretion to the body in response to an unknown stimulus, an imperfect product (or by-product) is formed and as an example suggested that an incompletely iodized thyroxine molecule may be formed at least as a part of the product. However, the administration of di-iodothyronine has not yet been demonstrated to have any such peculiar effect.

In addition to this possibility I should like to point out that in the conjugation of thyroxine in the body, as diagrammatically represented by Harington,[129] it is conceivable that the course of the series of reactions or the concentration of certain intermediate by-products with or without the benzene ring might be different under abnormal stimulation from those formed as a result of normal stimulation; for example, an amine compound might readily be formed in the presence of a low iodine concentration when the gland is working in response to the high stimulus that causes exophthalmic goiter. Under these conditions the synthetic formation of thyroxine is forced to proceed not only at an abnormally rapid rate but also frequently with a low concentration of iodine available. If such changes in conditions were made in the laboratory we should anticipate a difference in not only the quantity of the end-products but also in the quantity and possibly even in the character of

the intermediate by-products. One would not necessarily expect to find these by-products stored in the gland. In fact, an intermediate substance like tyramine, or one containing a tyramine radical, might be formed by the di-carboxylation of a tyrosine molecule and immediately be discharged into the circulation. Amines in general tend to have a toxic effect on the sympathetic nervous system. That some such or a similar abnormal by-product may be the factor in producing the exophthalmos and other characteristic symptoms, other than those due to hyperthyroidism, of the syndrome of exophthalmic goiter is rendered probable by the following experiments of Labbé and his associates and of Code and Essex.

Labbé and his associates (references 183-185) in 1931 presented before the French Academy of Science the results of an extensive series of experiments on the production of exophthalmos in animals. Their chief points may be summarized as follows: 1. Electrical stimulation of the sympathetic nerves produces protrusion of the eyeball (Bernard), but as it is accompanied by dilatation of the pupil it is not the same as in exophthalmic goiter, in which the pupil is not dilated. 2. One knows that hyperthyroidism produced by an excess of thyroxine rarely produces exophthalmos. Also, it is known that an excess of thyroxine is not necessary to produce it; however, it is possible that thyroxine plays the rôle of an adjunct and renders the conditions favorable for the production of exophthalmos by some other primary cause. 3. The sympathomimetic group of drugs differ profoundly in their action on the eyeball. Some, like epinephrine or adrenalone, produce powerful vasoconstriction but show little tendency to produce exophthalmos. Others like ephedrine, ephedrone, tyramine and para-methyl-phenyl-ethyl-amine cause marked protrusion of the eyeball. 4. Pilocarpine and hordenine cause a rapid regression of exophthalmos. 5. Thyroxine intensifies the action of some of these drugs in their power to produce exophthalmos.

Labbé and his associates also demonstrated that successive injections of thyroxine, of pilocarpine and of ephedrine will produce marked exophthalmos which persists and is accompanied by phenomena of excitation of the sympathetic and parasympathetic system.

Code and Essex from Mann's laboratory gave a demonstration of the production of exophthalmos in dogs at the recent meeting of the American Physiological Society (1935). They removed the superior orbital plate, exposing the fascia bulbi; on stimulation of the central end of the cut vagosympathetic chain a marked constriction of the fascia bulbi was clearly seen which caused marked protrusion of the eyeball. The effect was more pronounced following section of the cervical portion of the cord. Isolated strips of the fascia bulbi in Ringer's solution responded to epinephrine by definite contraction. Histologic preparations of the fascia reveal the presence of smooth muscle fibers. Further experiments along this line will be awaited with interest.

I shall now refer to a few of the more recent investigations on the thyroglobulins, especially those which have a clinical interest. A more detailed study of these and the substitution products of thyronine and the various isomers of thyroxine in which the halogen atoms are varied can be obtained in Harington's book;[129] little is yet known, however, of their detailed physiologic activity.

Hektoen, Carlson and Schulhof (1923) demonstrated thyroglobulin by the precipitation method in the lymph from the thyroid gland and later (1924) in the venous blood from the thyroid. Since 1931 Barnes, working in Carlson's laboratory, has published, with collaborators, several brief articles (references 19, 20, 21 and 23) on the physiologic activity of thyroglobulin; he found that it was absorbed undigested from closed loops of the intestine of anesthetized dogs. Barnes, Bueno and Jones also (1934) split thyroglobulin into an acid-insoluble and an acid-soluble fraction by treatment with pepsin for from twelve to twenty-four hours. These fractions contained about equal amounts of iodine, although the acid-soluble fraction contained about four times as much thyroxine (by the method of Leland and Foster); both fractions, however, had about equal activity in elevating heat production, which was approximately the same as from desiccated thyroid containing the same amount of iodine. However, the criteria used by Barnes do not necessarily indicate that the two split products would be equally effective in the treatment of myxedema.

Harington and Salter (1930) obtained as the end-product of enzymic digestion of thyroglobulin a thyroxine polypeptide which is more soluble than thyroxine and like it can be given intravenously. Lerman and Salter showed, on control myxedematous patients in Mean's clinic at the Massachusetts General Hospital, that thyroxine polypeptide produces the same calorigenic action by mouth as when given intravenously. It is therefore a convenient substance by which to compare the various thyroid compounds that cannot be injected intravenously with thyroxine, which can be given only intravenously. Lerman and Salter also showed that di-iodotyrosine peptone obtained by peptic digestion of thyroglobulin is probably inactive. They concluded that no calorigenic activity is lost in the isolation of thyroglobulin from whole thyroid gland but that di-iodotyrosine loses its activity in the first stage of digestion of thyroglobulin.

Gutman, Benedict and Palmer (1931 and 1932) analyzed by the method of Leland and Foster the thyroxine content of various thyroid preparations on the market and found a variation between the highest and lowest of 259 per cent. Means, Lerman and Salter [252] (1933) assayed the effect of various commercial preparations of thyroid gland on myxedematous patients and found that their calorigenic action depended on the total organic iodine rather than on the thyroxine-iodine content. As Harington and Randall (references 131 to 133) showed that apparently the whole of the acid-soluble iodine in thyroid compounds is 3:5 di-iodotyrosine (which is calorigenically inactive) and only the acid-insoluble part is thyroxine, the mechanism by which di-iodotyrosine assumes calorigenic properties when linked to the amino-acids in iodothyroglobulin is still a mystery.

Thompson and his associates [325] at the Presbyterian Hospital, Chicago, carried out a valuable series of comparisons of the effect of different thyroxine compounds on the heat production of myxedematous patients. Their work is summarized in table 4.

Salter, Lerman and Means [299] (1935) showed that the calorigenic action of the optically active isomers of thyroxine (the d- and l-thyroxine) is essentially identical when assayed on myxedematous patients. They found that the daily intravenous administration of 0.75 mg. of d- or l-thyroxine produces the same effect as a similar amount of the racemic (natural or synthetic) thyroxine and also that it is equivalent to the effect produced by the oral administration of 1 mg. of thyroxine polypeptide containing the same amount of iodine (0.5 mg.).

TABLE 4.—*Effects of Various Compounds of Thyroxine on Heat Production* *

Medication†	Iodine Content	Number of Parts	Number of Administrations	Average Change in Basal Metabolic Rate, Points	Average Change in Basal Metabolic Rate in Terms of Response to Intravenous Injection of Thyroxine
10 mg. of thyroxine in alkaline solution intravenously	6.5	6	8	32	100
10 mg. of thyroxine by mouth suspended in water.....	6.5	4	4	2	6
10 mg. of thyroxine into duodenum	6.5	3	3	1	3
10 mg. of thyroxine by mouth in monosodium salt in tablets...	6.5	6	6	7	22
10 mg. of thyroxine by mouth in alkaline solution	6.5	5	5	20	63
2.83 Gm. of desiccated thyroid by mouth in tablets.....	6.5	5	5	22	69

* Reported by Thompson, Thompson, Taylor and Alper.
† The doses used were 10, 30, 40 and 100 mg.

The problem of why desiccated thyroid has a greater calorigenic action and also protects better against cyanide poisoning (Hunt acetonitrile test) than does thyroxine is therefore not explained on the basis of a more active isomer of thyroxine.

Because of these unexplained discrepancies between the thyroxine analysis of preparations of desiccated thyroid (Gutman, Benedict and Palmer) and the variation in effectiveness in the calorigenic action of thyroxine itself, as compared with desiccated thyroid, the recommendation of Means, Lerman and Salter seems sound, namely, that the present method of standardization on the total content of organic iodine as now recommended by the United States Pharmacopoeia be maintained until these discrepancies are more clearly understood.

Abelin (references 3 to 5) recently announced (1933 and 1934) that a thyroxine-like substance can be isolated in impure form from artificially iodized protein. It can be given by mouth and causes an increase in heat production even in thyroidless rats. He concluded that

there is in the organism outside the thyroid a substance which produces an action similar to thyroid substance, which he has named homothyroxine. Further information about this substance will be awaited with interest.

At the meeting of the American Society for Clinical Investigation in May 1935, Salter presented as a preliminary communication his studies on the synthesis of an artificial protein containing iodine which resembled natural thyroglobulin. He furnished me the following abstract of this important work:

Means, Lerman and Salter have determined the calorigenic effect of a series of thyroxine derivatives, namely, racemic crystalline thyroxine, crystalline l-thyroxine, crystalline d-thyroxine glycyl-thyroxine (di-peptide), thyroxine polypeptide (from sheep), thyroxine peptone (from man), whole desiccated thyroid (U. S. P.), thyroglobulin from patients with exophthalmic goiter and thyroglobulin from patients with multiple colloid adenomatous goiter. In terms of total iodine all these preparations yielded essentially identical responses when administered according to a standard procedure to patients with full-blown myxedema. Because they doubted the physiologic validity or therapeutic appropriateness of assays obtained following a single massive dose, these investigators (1) used daily doses containing 0.5 mg. of total organic iodine and (2) administered each drug in a manner which insured maximal assimilation. In consequence, the patients' basal metabolic rates became normal in about two weeks.

It was found that whole thyroid produced much more calorigenic effect than would the thyroxine which it contained. In order to corroborate further the effectiveness of both (*a*) the acid-insoluble or thyroxine fraction and (*b*) the acid-soluble or di-iodotyrosine fraction when combined in thyroglobulin, purified human thyroglobulin was digested with pepsin, and the digested material was separated into (*a*) the thyroxine peptone and (*b*) the di-iodotyrosine peptone. The thyroxine peptone (*a*) was found to be precisely as active calorigenically as the thyroxine which it contained. The di-iodotyrosine peptone (*b*) was ineffective in standard doses. Nevertheless from this relatively inert human material (*b*) Salter was able to obtain by peptic synthesis an artificial protein which contained iodine which resembled natural thyroglobulin and which was equally effective calorigenically in standard doses. The peptic synthesis was achieved by a modification of the procedure described by Wasteneys and Borsook. Suprisingly, the new artificial protein contained an acid-insoluble fraction (after alkaline hydrolysis) which behaved chemically like thyroxine.

ENDEMIC GOITER

Although the value of iodine in the treatment of goiter had, as I have already mentioned, been known for a long time, it was Prevost in 1849 who was apparently the first to suggest that goiter is caused by a deficiency of iodine (and bromine). Following this suggestion Chatin [55] (1851-1854) carried out extensive investigations on the presence of iodine in water, soil, plants and animals; he concluded that its deficiency is the cause of goiter and recommended to the French Academy that in districts where goiter was endemic it could be prevented by the addition of iodine to the water supply. His recommendations were not accepted,

apparently in part on the ground that his own figures for iodine in the water supply did not always correspond to the intensity of the incidence of goiter.

No further important investigations were made until McCarrison [209] in 1902 instituted his studies on goiter in India, especially in the Himalayan mountains. In the Gilgit Fan district there were eight adjacent villages; these were situated along the course of unprotected water channels where the people were primitive and dependent on their own local produce, which was of the same kind in all the villages. The incidence of endemic goiter in the first village was 11.8 per cent, and in the last village down the stream 45.6 per cent; in a ninth village, which received its water supply from a different source, the natives were relatively free from goiter. At that time the iodine content of the soil and water was not known, but it was determined later and found not to vary in the different villages. In 1906, 1907, 1908 and 1909 McCarrison (references 210 to 215) produced goiter in young men (volunteers) who were new arrivals in these villages. To produce goiter he used the sediment from the water as it issued from the last village. The men were divided into two groups: To one group was given to drink each morning before breakfast about 6 ounces (177 cc.) of this material suspended in water which was not boiled; to the other group the same amount was given, but after the mixture had been boiled. Of 31 men who drank the unboiled suspended matter 21 had no change in the thyroid gland; 10 had noticeable goiter, and 5 had a transitory swelling. Of 31 men who drank the boiled suspended matter none had any increase in size of the thyroid gland. Those in whom goiter developed (including McCarrison himself) had associated with this condition a throbbing in the neck and feelings of fulness and discomfort. McCarrison concluded that there is a contagium vivum which is the responsible factor in the production of goiter.

Since these classic experiments McCarrison has continued to investigate, and in later years to supervise many investigations on, the cause and prevention of goiter in India. His experimental work has been directed along lines planned to elucidate the influence on the development of goiter in animals of such factors as filthy cages, the effect of unbalanced diet lacking or having an excess of various essential elements, the influence of vitamins and so forth, together with the influence of iodine on these various factors. He has amply demonstrated that both diet and filth (bacteria) play an important rôle in favoring the development of goiter and that they are more goitrogenic if and when the intake of iodine is low but are usually less goitrogenic or entirely innocuous in the presence of an excess of iodine.

McCarrison [217] in his address before the First International Conference on Goiter in Bern (1927) presented an excellent summary of

his experimental work and a clear discussion of the evidence for and against the two chief theories promulgated to account for endemic goiter in its various forms: (1) the theory of iodine deficiency and (2) the infectious or toxic theory. He concluded that the truth lies in a judicious blend of both. As there are various types of "simple goiter" which may prevail in the same locality, and as some persons are capable of being benefited by the prophylactic use of iodine, some are not benefited and some may be harmed by it, he is opposed to the indiscriminate use of iodine as a prophylactic measure as both unscientific and dangerous.

By this, as one gathers from his more recent papers, McCarrison does not believe (and I think all would agree with him) that only iodine should be used to control the development of goiter, but that, in addition, all contributory factors such as insanitary water supplies and foul conditions as well as deficiencies in the diet—so well brought out in his more general studies in deficiency disease—should simultaneously be remedied. He would consider it unscientific simply to give large quantities of iodine to minimize the effect of such conditions without at the same time attempting to improve them.

McCarrison has devoted the major portion of his life's work to the study of endemic goiter. Marine, in this country, has done the same thing. Many of Marine's contributions to the knowledge of the cause and means of prevention of endemic goiter are classic investigations. As with McCarrison, I cannot begin to do justice to their manifold ramifications but must limit myself to those researches which laid the foundation for the practical and effective prophylactic prevention of endemic goiter on a large scale. Marine can feel that his work has been a great success and that the results of his labors will prove an ever greater boon, not only to man himself, but to man's domestic animals.

In 1907, 1908, 1909 and 1917 Marine (references 222, 234, 238 and 244) published a series of papers on the relation of iodine to the structure and diseases of the thyroid gland, the following being his most important points: 1. All thyroid hyperplasia is anatomically, chemically (iodine) and histologically the same. 2. Iodine is necessary for normal thyroid activity. 3. The iodine control of the thyroid gland varies inversely with the degree of hyperplasia. 4. Iodine is rapidly taken up by the thyroid. 5. Exophthalmic goiter is constantly accompanied during the progressive stage of the disease by thyroid hyperplasia, and the iodine content varies inversely with the degree of hyperplasia.

About 1907 an epizootic of what appeared to be carcinoma of the thyroid broke out in many of the state and national fish hatcheries. This disease was investigated by Gaylord and Marsh and by Marine and Lenhart;[240] Gaylord was inclined to believe that the disease was carcinoma due to an infectious factor, whereas Marine and Lenhart

(1910) proved that the disease was endemic goiter, similar to that which they had studied in mammals, and showed that it could likewise be controlled by adding compound solution of iodine to the water in the fish troughs. Gaylord confirmed the beneficial effects of iodine but also demonstrated that mercury and arsenic or the institution of sanitary conditions would interrupt the progress of the disease and restore the thyroid epithelium to a condition approximating normal, and he was particularly impressed, as McCarrison had been in his study, with the fact that the goiter (or carcinoma [?] of the thyroid) was most prevalent under insanitary conditions.

In 1888 Halsted is cited in a preliminary report by Welch as having pointed out that after partial removal of the thyroid gland in dogs compensatory hypertrophy developed in the remnant of the gland not removed which resembled somewhat the diffuse hypertrophy found in cases of exophthalmic goiter but without any of the constitutional symptoms of that disease. Halsted [117] published the report of these experiments in detail in 1896. This method of producing compensatory hypertrophy has proved a valuable experimental method in the study of the etiology of different forms of goiter, and it was used by Loeb in his series of experiments by which he finally proved that extracts of the anterior lobe of the pituitary gland would produce in animals a syndrome closely resembling exophthalmic goiter in man; this will be described in detail later. However, in 1914 Halsted [124] attempted to repeat these experiments but was unsuccessful, and he wrote about them to Marine, who was at that time in Vienna. Marine replied and asked whether iodine had been used in the laboratory. Halsted answered that it had been used as a disinfectant of the skin on some of the dogs but not on all, and he was somewhat skeptical of that being the cause, although subsequent developments indicated that the presence in and general use of iodine around the laboratory are sufficient to permit the development of compensatory hypertrophy.

As a result of these studies, and of many others that I do not have space to mention Marine and Kimball [234] began in 1917 a survey of the incidence of goiter in the school children of Akron, Ohio, from the fifth to the twelfth grades, inclusive, and instituted a carefully planned prophylactic procedure. A preliminary report of the beneficial effects secured appeared in 1918,[156] and the fourth [235] report, which was more extensive, in 1920. The results obtained are given in table 5.

The idea of Marine and Kimball [236] of initiating a prophylactic program for the prevention of endemic goiter in school children was a brilliant conception, as it avoided the possible danger of giving iodine to adults who already had goiter. As a result of its successful application to the school children of Akron popular resistance and prejudice to a more general prophylactic program was overcome in Michigan and

iodized table salt was generally introduced on the market in that state. McClure recently reported favorable results in Michigan from the use of such iodized salt.

Likewise, in Switzerland, where the dangers of *Jod-Basedow* are the greatest the prophylactic use of iodine has, wherever carried out, produced most striking results, as reported in detail by Eggenberger and in a more general way by de Quervain [287] who has carefully and conscientiously guided the Swiss program. In Germany Fischler maintained that only ungrounded timidity prevented the rapid and complete control of endemic goiter, with all its secondary ill results of cretinism, mental and physical deficiency, stillbirth and so forth. As a result of the enthusiastic but sound efforts of Fischler and of other public health officials there is an indication that a national prophylactic program

TABLE 5.—*Summary of Record of Pupils Taking and Not Taking Iodine* *

Condition of Thyroid Gland	Taking		Not Taking	
	Total	Percentage	Total	Percentage
Normal				
Unchanged	906	99.8	910	72.4
Increased	2	0.2	347	27.6
Slightly enlarged				
Unchanged	477	41.9	698	72.8
Increased	3	0.3	127	13.3
Decreased	659	57.8	134	13.9
Moderately enlarged				
Unchanged	29	20.3	57	64.0
Increased	0	0	21	23.6
Decreased	114	79.7	11	12.4
Total	2,190		2,305	

* Reported by Marine and Kimball.[285]

may be initiated in Germany to the end that "the nation be not deprived of the eugenic improvement that can occur in their goiter districts." In addition to the favorable results of goiter prophylaxis just referred to there have been many others, but of these I can only mention the very convincing results obtained by the Goiter Committee of The Netherlands as abstracted by Reith. The successful result of prophylactic measures wherever tried with practically no harmful effects has convinced most of the leaders of the medical profession of the safety of carefully supervised prophylactic methods. In recent years other lines of investigation have also led to the same conclusion—largely by the destruction of the fear of the proper use of iodine.

RECENT WORK ON THE EXPERIMENTAL DEVELOPMENT OF GOITER

Experimental Production by Cyanide of Simple (Endemic Type) Goiter in Animals.—In previous sections I have referred to the earlier experimental work on endemic goiter. A consideration of the recent

work can be conveniently begun with the accidental observation by Chesney, Clawson and Webster (1928) that goiter tended to develop in rabbits in the laboratory at Johns Hopkins which were fed a diet containing a large quantity of cabbage. In the study of this phenomenon these investigators found that enlargement of the thyroid was accompanied by a lowering of the heat production and definite cellular hyperplasia and, further, that the administration of iodine raised the heat production to the normal level and prevented thyroid hyperplasia.

Marine, Baumann and Cipra (1929) confirmed these facts and demonstrated that boiling or steaming the cabbage for thirty minutes increased its goitrogenic effect, that steamed cabbage from which 60 per cent of its weight has been removed as press-juice was practically as effective, that the press-juice itself was ineffective and that winter cabbage was more effective than summer cabbage. They concluded that the goitrogenic agent is not hexuronic acid (cevitamic acid, introduced as ascorbic acid) and also that goiter is probably not due to an absolute deficiency of iodine but only to a relative deficiency. On the other hand, drying in a current of air in vacuo causes loss of the goitrogenic agent (Marine, Baumann, Webster and Cipra,[229] 1930); it can be extracted with ether or other ethereal solvents but only slightly extracted by water (Baumann, Cipra and Marine, 1931).

Since all brassicae (cabbage, brussels sprouts and so forth) produce goiter and since mustard oils (isothiocyanates) are the most characteristic constituents of these plants, it was thought the goitrogenic activity might in some way be connected with these substances or their cyanide precursors. Therefore, Marine, Baumann, Spence and Cipra [228] (1931) investigated all the more common cyanide compounds and found that they all had this goitrogenic power, but that acetonitrile (methyl cyanide) produced the greatest reaction and the aromatic nitriles the least reaction; cyanamide produced only a slight reaction and sodium thiocyanate none. Marine and his co-workers concluded that these substances acted by depressing oxygen consumption and thereby increased the demand for thyroid activity.

Marine, Rosen and Cipra (1933) have shown that chronic, progressive, bilateral exophthalmos could be produced in more than 150 prepubertal rabbits maintained on a diet of alfalfa hay and oats by the daily intramuscular injection of from 0.05 to 0.1 cc. of methyl cyanide. Fresh vegetables fed the rabbits markedly inhibited its development. Exophthalmos may appear as early as the fourteenth day and as late as the sixtieth day after the beginning of the injections of cyanide. Males are much more susceptible, and some breeds (Dutch) are more susceptible than others (Belgian). The degree of exophthalmos obtained has been highly variable in rabbits of the same age, sex and breed, but it is always proportional to the degree of thyroid hyperplasia

(goiter) present. Removal of one superior cervical ganglion permanently abolished the exophthalmos on that side in six animals, but curettage of the medulla of both adrenal glands was without effect. Thyroidectomy in thirteen prepubertal rabbits hastened the onset of exophthlmos and increased its features after it developed.

Marine and Rosen (references 231 and 243) (1934) have been impressed with the fact that chronic and progressive exophthalmos can now be readily produced in immature animals of susceptible species by the injection of pituitary extracts and of cyanides (preferably methyl cyanide) into rabbits maintained on a diet of alfalfa hay and oats. They expressed the belief that both these means of production depend on two factors: (1) the thyrotropic hormone of the anterior lobe of the pituitary gland, in the one case by passively supplying it and in the other by stimulating the pituitary gland to produce it and (2) the existence of a relative thyroid insufficiency. The maintenance of a normal thyroid by the administration of iodine or thyroxine prevents exophthalmos caused by cyanide and pituitary extract. This indicates that normally there is a delicate physiologic balance between the need for thyroxine and the thyrotropic hormone. As regards therapy, iodine and desiccated thyroid appear to be the only logical remedies at present available, but Marine and Rosen do not believe that the results are very promising either in human exophthalmic goiter or in the experimental exophthalmos of rabbits.

Marine, Baumann, Webster and Cipra [230] (1933) followed up the inhibiting effect of fresh plants previously noted by them on the goitrogenic properties of cabbage. They found that lawn grass, fresh alfalfa, skunk cabbage and steamed cabbage press-juice are antigoitrogenic. Washing brassicae with water improves their goiter-producing action, probably by removal of the goiter-preventing substances. They found that the antigoitrogenic effect of plant juice varies with the amount of reducing substance present other than glutathione. Some of the antigoitrogenic extracts contain iodine, while others do not; they are easily soluble in water or in ethyl alcohol and are precipitated by lead acetate at a p_H of from 6.8 to 7 and are partially destroyed by exposure to air and by steam at 100 C. The antigoitrogenic agent might be hexuronic acid, but it could not be glutathione. Marine, Baumann and Rosen later (1934) published the results of experiments which they interpreted as indicating that this antigoitrogenic factor actually is cevitamic acid (hexuronic acid, ascorbic acid).

Baumann, Sprinson and Metzger (1933) demonstrated that in the absence of the thyroid only 3 to 5 per cent of the cyanide of administered acetonitrile is converted into thiocyanate in rabbits, whereas with the thyroid gland intact from 27 to 35 per cent of the cyanide is transformed. The catalyzing influence of the thyroid gland is specific for

acetonitrile (methyl cyanide) and does not alter the amount of benzene cyanide or potassium cyanide converted; hence it is concerned with demethylation only.

Space prevents reference to the experiments of other observers who have confirmed many of the essential facts obtained by Marine and his associates or to those who have brought out preliminary evidence of the existence of other goitrogenic agents. That there is a difference in the reaction of different species to the influence of cyanides in producing the endemic type of goiter is indicated by the fact that Loeb and Friedman (personal communication to the author) have been unable to produce goiter in guinea-pigs by the administration of acetonitrile.

Experimental Production by Extract of the Anterior Lobe of the Pituitary Gland of a Syndrome in Animals Resembling the Syndrome of Exophthalmic Goiter in Man.— Loeb [192] demonstrated in 1921 that tethelin (the active principle of the anterior lobe of the pituitary gland) has no inhibitory effect on compensatory hypertrophy of the thyroid gland, while Loeb and Kaplan [199] in 1924 found that the feeding of tablets of the anterior lobe of the pituitary gland (Armour) prevented compensatory hypertrophy in guinea-pigs. It was well known that hypophysectomy caused an apparent reduction in the activity of the thyroid gland.

After being stimulated by the work of Uhlenhuth and Schwartzbach on salamanders, Loeb was able to announce at the meeting of the St. Louis branch of the Society for Experimental Biology and Medicine in May 1929 that he and his associates [195] had obtained a hormone by making an extract of the anterior lobe of the pituitary gland which would produce compensatory hypertrophy of the thyroid gland of guinea-pigs, accompanied by loss of weight, thus indicating that there was an increased elimination of the thyroid hormone. Subsequent studies from his laboratory confirmed and extended these observations. Other investigators also contributed many important facts, the first of whom was Aron,[13] who six months after Loeb and likewise on the guinea-pig (which Loeb in previous studies on compensatory hypertrophy had found to be a most favorable species) reported similar results at the meeting of the Société de biologie in November 1929. The evidence which has accumulated in the last five years, in great part from Loeb's laboratory, indicates that the syndrome produced in animals by the injection of the hormone of the anterior lobe of the pituitary gland is similar to (and possibly identical with) the syndrome of exophthalmic goiter in man. Even if the syndromes are comparable it does not necessarily follow that the disease of exophthalmic goiter in man is necessarily due to overactivity of the anterior lobe of the pituitary gland—it might be due to the introduction into, or formation in the body of, some other

as yet unknown substance which has the power to stimulate the thyroid gland in a similar manner.

At present an instructive series of articles is appearing under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association (references 62, 91, 225 and 317) on the general subject of the physiology of the organs of internal secretions, of which eight are devoted to the different physiologic functions of the anterior lobe of the pituitary gland and its various hormones, with complete references to the literature without, however, greatly stressing the significance of the thyroid-stimulating hormone in elucidating the problem of thyroid disease as a whole. It is now appropriate to lay the specific groundwork, the broad foundations having been presented in the previous section, on which the discovery of the thyroid-stimulating substance was made.

As I have pointed out, Marine and Lenhart (references 237 and 239) first in 1909 and in their subsequent work repeatedly stated that the administration of iodine in any form would reduce or "involute" hyperplasia of the thyroid if present in animals or prevent its development as compensatory hypertrophy following extirpation of considerable portions of the thyroid gland; this work, as has been shown, led to their work on the prevention of goiter.

About 1918 Loeb at Washington University, St. Louis, began experimental work to study the effect of the many different factors influencing the production of hypertrophy of the thyroid gland and used as his test object the compensatory hypertrophy which readily develops in guinea-pigs following the removal of considerable portions of the thyroid gland. Loeb reported [191] in 1920 that the administration of iodine does not diminish the intensity of compensatory hypertrophy and hyperplasia but on the contrary intensifies it. A marked increase in mitotic figures and a slight increase in the size of the cells were demonstrated. Loeb showed that the active principle of the anterior lobe of the pituitary gland known as tethelin has no effect on the development of the hyperplasia but that the administration of thyroid tablets has a marked inhibitory effect. Loeb and Kaplan [199] (1923 and 1924) showed that the feeding of anterior lobe of the pituitary gland (Armour) prevents a marked or even a moderate degree of hypertrophy.

Marine [225] (1926) suggested that Loeb's "failure" to obtain "protection" by potassium iodide against compensatory hyperplasia was due to removal of too large a portion of the thyroid gland and referred to the original experiment of Marine and Lenhart [239] (1909) in which protection was obtained if not more than three fourths of the gland were removed.

Loeb [193] (1926) stated more definitely, on the basis of a large number of experiments, that there was no question that potassium iodide does

not prevent or even diminish the compensatory hypertrophy of the thyroid gland in guinea-pigs, and distinguished between two types of response: (1) the effect on the part of the thyroid to make a normal amount of thyroxine with a low supply of iodine, and (2) the effect of some unknown stimulus which forces the thyroid to make and discharge an excess amount of thyroxine.

Marine, Deutsch and Cipra [233] (1927) replied that iodine administered in any form and in every manner will cause involution of physiologic hyperplasia of the thyroid as well as prevent its occurrence in all orders of animals in which it has been studied: fish, birds, mammals and man. They showed that in experiments on 18 normal rabbits large doses of iodine caused a drop in the basal metabolic rate in 5, a slight increase in 2 and no change in 11. The discrepancy in the action of iodine was finally cleared up by Gray and Loeb (1928), who showed it to be due to a temporal relationship, because the hypertrophic and hyperplastic changes in guinea-pigs reached a maximum in a certain time and then receded to a normal or subnormal level. Cordonnier (in Loeb's laboratory, 1928 and 1929) demonstrated that notwithstanding the stimulating effect on the gland by causing transient hypertrophy and hyperplasia, potassium iodide does not lead to an increased output of thyroxine, as it produces no noticeable alteration in the heat production.

In 1927 an illuminating paper appeared by Uhlenhuth and Schwartzbach on the morphology and physiology of the thyroid gland of the salamander, which is so important that I shall briefly summarize it. In amphibians thyroid function consists of two main phases: (1) the elaboration of the active secretory product of the thyroid gland, the colloid, in the thyroid cells—the excretion of the colloid from the cells into the lumen of the follicles and the storage of the colloid in the follicles and (2) the excretion of the colloid from the follicles into the circulating blood. The presence of these two distinct phases is the most important characteristic. After the secretion product is formed it lies in a completely closed lumen of the follicles, and in order to effect its excretion into the circulation of the blood a special releasing-mechanism is required. During the larval period the activities of the thyroid are confined entirely to those of the first phase; the second phase, or discharge, develops suddenly at the end of the larval period and is the immediate cause of the metamorphosis. The activities of the developmental phase are elementary properties of the thyroid organ and are controlled by factors similar in nature to those controlling the activities of other glands; display of the functional phase can be effected only by the action of an extrinsic releasing-mechanism. Proceeding from a neurocirculatory hypothesis, Uhlenhuth and Schwartzbach found that no experimental procedures directed toward influencing the nervous system will hasten metamorphosis or bring about discharge of the thyroid

secretion. On the other hand, desiccated substance of the anterior lobe of the pituitary gland (Armour) will hasten metamorphosis and start the thyroid gland through the whole cycle of functional changes characteristic of thyroid glands of normal metamorphosing larvae—increase in the size of the cells, which become columnar, and a massing of the secretion granules at their apex.

In mammals there is, of course, no metamorphosis and therefore no normal, sudden releasing-mechanism (except possibly some similar mechanism in hibernating animals), but the fact that the thyroid gland of any species is susceptible to being suddenly thrown into extreme activity by a chemical stimulant (in this case presumably the pituitary hormone) appears to me of profound significance.

This paper of Uhlenhuth and Schwartzbach, as Loeb [194] remarked, stimulated him to reinvestigate the effect of the anterior lobe of the pituitary gland on the compensatory hypertrophy of guinea-pigs, and, thinking that some other substance might be present in the preparations of the anterior lobe previously used, he made acid and alkaline extracts from dried and powdered anterior lobes of the pituitary gland and found that both extracts will produce hypertrophy of the thyroid gland accompanied by loss of weight and other signs suggesting an increased elimination of thyroid hormone. This discovery was announced by Loeb and Basset (references 195 and 196) at the May 1929 meeting of the St. Louis Branch of the Society for Experimental Biology and Medicine. Silberberg, in October 1929, from Loeb's laboratory, confirmed and amplified these observations and reported that the stimulation of the hyperplasia and hypertrophy of the acinal epithelium was very marked, with rapid absorption of the colloid, and that the histologic picture produced resembled that of exophthalmic goiter and was very different from the comparatively mild hypertrophy and hyperplasia that Loeb had demonstrated in from fifteen to twenty days following the administration of potassium iodide. When both were given together a mosaic picture was produced but no summation effect; on the contrary, there was possibly a diminished effect of the extract of the anterior lobe of the pituitary gland. It was therefore concluded that the mechanisms which produce the effects are probably different.

Aron,[13] at the meeting of the Société de biologie on Nov. 15, 1929, announced that extracts of the anterior lobe of the pituitary gland will produce hypertrophy of the thyroid epithelium in guinea-pigs, with absorption of the colloid, whereas extracts of other organs do not do this, and suggested that the pituitary gland controls the activity of the thyroid.

Siebert and Smith (references 312 and 313) (1930), from Loeb's laboratory, showed that the daily subcutaneous injection of either acid or alkaline extracts of the anterior lobe of the pituitary gland will

cause a rise in the basal metabolic rate which may reach a maximum of + 60 per cent in the first ten days and then return to a level of about + 15 per cent, whereas the oral administration daily of 5 grain (0.3 Gm.) pills of a substance of the anterior lobe of the pituitary gland prepared by them caused a slight gradual rise to + 20 per cent with a gradual return to normal. However, the oral administration of 5 grains a day of Armour's preparation caused a gradual rise to approximately + 60 per cent in about thirty days, but there was no tendency for the basal metabolic rate to become lower. Siebert and Smith [3,14] later, in 1930, showed that the rise in the basal metabolic rate caused by Armour's tablets of the anterior lobe of the pituitary gland occurred in the same manner even after partial or complete thyroidectomy. On the other hand, no rise occurred after thyroidectomy when their own extract of anterior lobe of the pituitary gland was injected, and they therefore concluded that the rise caused by their extract was dependent on the hypertrophic changes produced by it in the thyroid gland.

Cordonnier, in Loeb's laboratory, in 1929 showed that the administration of potassium iodide to normal guinea-pigs did not increase the basal metabolism; neither did it exert any noticeable effect on the rise in basal metabolism caused by the oral administration of thyroid tablets. Loeb had shown in 1920 that thyroid tablets given by mouth not only prevent compensatory hypertrophy of the thyroid gland in guinea-pigs but in addition lower the activity of the thyroid gland below normal. Correspondingly, Gray and Loeb (1928) and Gray and Rabinovitch (1929) found that thyroid tablets, when administered orally, lower the number of mitoses in the normal thyroid gland of guinea-pigs.

Aron [10] in January 1930 made a further report on the histologic changes in the thyroid gland produced by the injection of extract of the anterior lobe of the pituitary gland and in April [11] of the same year found that these changes could be prevented by the simultaneous injection of thyroxine. Later Loeb, Basset and Friedman (1930) also demonstrated that the administration of thyroid tablets diminishes the hypertrophy which is caused by extract of the anterior lobe of the pituitary gland. The fact that the thyroid can be put at rest by the administration of thyroxine is in harmony with the previous clinical observation of Plummer (1922; 1925).

Aron [12] and Aron and Klein [15] (1930) became interested in using the hypertrophic response of the thyroid of the guinea-pig to known extracts of the anterior lobe of the pituitary gland as a test object for the presence of this hormone in urine, blood and other fluids. On the assumption that such a reaction is indicative of the presence of the hormone of the anterior lobe of the pituitary gland in the blood and urine. Aron reported its presence in human urine. He then became interested

in following up the clinical application of this test, which he reported in a series of papers which appeared mostly in *Comptes rendus des séances de la Société de biologie* from 1930 to 1934. Castillo and Magdalena (1932), in Houssay's laboratory, did not find the test sensitive enough for diagnostic purposes, and its value for this purpose was absolutely denied by Krogh and Okkels [178] (1933). This phase of the subject is, however, outside the province of this review.

Closs, Loeb and MacKay (1931 and 1932) showed that the changes in the concentration of iodine, and especially in the concentration of the organic iodine, in the thyroid gland and in the circulating blood following the administration of extract of the anterior lobe of the pituitary gland corresponded to the changes found in the thyroid gland in cases of exophthalmic goiter. Loeb and Friedman [198] (1932) were the first to notice that exophthalmos develops in guinea-pigs following the use of extract of the anterior lobe of the pituitary gland. Since then this fact has been confirmed repeatedly and for nearly all types of laboratory animals used.

Siebert and Thurston (1931 and 1932) demonstrated that the increase in heat production caused by extracts of substances of the anterior lobe of the pituitary gland was much diminished by the simultaneous administration of potassium iodide. Friedgood (1934) showed that this effect of iodine was frequently only temporary and varied with dosage. On the other hand, the increase in heat production following the administration of pituitary substance (Armour) was not lowered but rather somewhat increased by the administration of potassium iodide, thus definitely showing that there is a difference in the calorigenic action of these two substances. Houssay and Rietti (1932) confirmed the increased metabolism in rats, by means of Asher's anoxemia test, by showing that rats after receiving injections of extract of the anterior lobe were more sensitive to lower concentrations of oxygen than were untreated rats; they obtained the same results later in guinea-pigs.

Houssay, Biasotti and Magdalena (1932) by injection of extract of the anterior lobe produced in dogs the hypertrophy and hyperplasia in the thyroid gland with absorption of the colloid that had been found by others in guinea-pigs. They were able to obtain this reaction in both normal and hypophysectomized dogs and also found that transplanted thyroid tissue responded in the same way. This reaction was in all instances prevented by the feeding of thyroid extract.

Benedict and Hommans (1912) showed that the heat production diminished after hypophysectomy in dogs, and since C. E. Smith's work in 1927 it has been known that hypophysectomy produces atrophy of the thyroid gland and an accumulation of colloid with a decrease in the size of the acinal cells (as pointed out in recent reviews

on the pituitary gland in *The Journal of the American Medical Association*), but in 1932 Houssay, Mazzocco and Biasotti added one important point, namely, that this resting condition of the gland was accompanied by an increase in the concentration of iodine of the gland.

Byars, Friedman, Siebert and Loeb (1932) showed that there was no variation in the activity of extract of the anterior lobe of the pituitary gland from cattle depending on the season of the year in which the glands were obtained. Houssay, Novelli and Sammartino (1932) found no change in the effectiveness of the extract even if the thyroid glands of the animals had been removed as long as a month and a half before the pituitary gland was obtained.

The experiments of Marine and his associates [242] are very interesting in that these investigators were able to produce exophthalmos in a few thyroidless guinea-pigs by the administration of extract of the anterior lobe, and also in rabbits by the administration of cyanide. Friedgood also showed that exophthalmos from the administration of extract of the anterior lobe often gradually became more pronounced after the return of heat production to or below normal. They were of the opinion that these experiments indicate that there is some underlying similarity in the response of the thyroid produced either by extract of the anterior lobe or by cyanide; they suggested that this similarity indicates thyroid deficiency in both instances.

In 1933 Anderson and Collip [7] announced the preparation of a highly purified extract of the anterior lobe of the pituitary gland and confirmed the physiologic effects noted previously by the less highly purified extracts; their preparation gave complete replacement therapy and produced hyperplasia of the thyroid together with hyperthyroidism in hypophysectomized rats and dogs.

P. E. Smith [316] (1932 and 1933) noted that in hypophysectomized, thyroparathyroidectomized rats, skeletal growth was distinctly greater when thyroid extract was given together with extract of the anterior lobe of the pituitary gland than when extract of the anterior lobe was given alone; on account of this apparent synergistic action he suggested that both extracts be used in the clinical treatment of pituitary dwarfs.

Schneider and Widmann [308] (1932) presented evidence which they interpreted as indicating that the beneficial effect of iodine as a preoperative procedure is not explainable on the basis of a direct action of iodine on the thyroid-stimulating hormone. Grab (1933) not only showed that there was a decrease in colloid following the administration of extract of the anterior lobe but that, in addition, the concentration of both thyroxine and di-iodotyrosine in the colloid was decreased. Loeser found by the use of certain extracts of the anterior lobe that in addition to hypertrophy of the thyroid gland there was in some instances hypertrophy of the adrenal gland. The adrenal hypertrophy did not develop

if the thyroid gland had been removed. Collip, Anderson and Thomson (1933) were able to produce a separation of the adrenotropic from the thyrotropic hormone. Schmeckebier (1934) found that administration of the hormone of the anterior lobe in various forms increased the proliferative activity in the adrenal cortex in guinea-pigs.

Aron[14] showed in 1933 that extract of the anterior lobe, when injected into the amniotic fluid, caused hypertrophy of the fetal thyroid in the same way as in the gland after birth. Elmer (1933) showed that di-iodotyrosine was as effective as potassium iodide in preventing hypertrophy of the thyroid gland of guinea-pigs by extract of the anterior lobe of the pituitary gland. Artunde and Solari and Bueno and Barnes confirmed the previous observation of the increase in heat production following the administration of extract of the anterior lobe.

Anderson and Collip (1934) added the interesting observation that the sensitivity of rats to extract of the anterior lobe was increased by the injection of a staphylococcic vaccine. They investigated in more detail the development of resistance to extract of the anterior lobe which had been shown by Loeb and Friedman (1931 and 1932) to occur from its prolonged administration. They found that the heat production of hypophysectomized rats was reduced to approximately 26 per cent below the average normal. Following the continued administration of extract of the anterior lobe a similar decrease in metabolism, from the preliminary increase of 30 or 40 per cent to the low level of the hypophysectomized rat, stimulated them to investigate the cause of this peculiar loss of effectiveness in the extract of the anterior lobe. As a result they discovered that it was possible to obtain what they called an "antithyrotropic" substance from the serum of horses which had been treated for a long time with extract of the anterior lobe of the pituitary gland. This antithyrotropic substance of Collip and his associates does not seem to be related to the substance described by Blum under the term katechin, which has been reported to have a beneficial effect in the treatment of exophthalmic goiter; the reports concerning the value of katechin are still very meager and unconvincing.

Black (1934), working with catfish, found that the heat production was increased by the injection of extract of the anterior lobe if the fish were confined in a small aquarium without running water, but if there was a rapid exchange of water an increase in heat production did not develop. He also found that if fish not receiving injections were confined in a small aquarium with fish that had received injections hypertrophy of the thyroid would likewise develop in the former.

Friedgood in 1934 made a detailed study of the development of exophthalmos and hypertrophy of the thyroid together with the preliminary increase in heat production and the subsequent remission in the heat production following the continued use of extract of the

anterior lobe. In fact, he showed that in the late stages the heat production not only returned to normal but frequently decreased to below the original level. He found no consistent correlation between the histologic picture of the thyroid gland and the curve of heat production. His experiments were particularly clearcut from the point of view of demonstrating that the syndrome produced in guinea-pigs by extract of the anterior lobe is similar to (but not necessarily identical with) the syndrome in man known as exophthalmic goiter.

Thompson, Taylor, Thompson and Dickie in 1935 reported that the subcutaneous injection of extract of the anterior lobe into human subjects produced an increase in the basal metabolic rate in 24 of 39 patients. This increase, however, was only temporary in spite of the continued administration of the extract and in this respect resembled the results in animals. They found no increase from extract of the anterior lobe when it was given to patients with typical complete myxedema (thyroidless human subjects). In a patient with exophthalmic goiter the symptoms were markedly aggravated by the use of extract of the anterior lobe.

In addition to the various reports just noted there is a series of ten or more papers by Okkels and Marie Krogh and collaborators (1932 to 1934) in which excellent correlation is reported between alterations in the Golgi apparatus and the intensity of the symptoms in patients with exophthalmic goiter and those following the administration of extract of the anterior lobe to guinea-pigs. However, they found that these changes in the Golgi apparatus persisted after the remission which was known to develop following the prolonged use of iodine and pituitary extract, and they showed that the preoperative treatment of exophthalmic goiter with iodine (Plummer) does not influence the marked hypertrophy of the Golgi apparatus; they therefore concluded that the cellular hyperactivity probably continues unabated and assumed that the factor inducing this hypersecretion must be some extrathyroid principle and if so it must be a stimulant of nervous or humoral character.

SUMMARY

The evidence presented in this review indicates definitely that there are two different types of stimuli which, in the presence of the small amounts of iodine usually present in the laboratory diet, affect the thyroid gland in very different ways, producing in one instance a condition resembling endemic goiter in man and in the other a syndrome resembling the disease in man known as exophthalmic goiter.

The most important facts are: (1) that there is a substance (cyanide) which when administered to a susceptible animal favors the development of a diffuse colloid type of goiter and occasionally under

special conditions may cause slight exophthalmos in a limited group of susceptible animals but which produces no symptoms of hyperthyroidism, thus resembling (with the exception of the occasional slight exophthalmos just referred to) the early and milder forms of endemic goiter in man and like it can be prevented by an excess of iodine, and (2) that there is a substance (extract of the anterior lobe of the pituitary gland) which when administered to several species of laboratory animals produces a thyroid-stimulating effect characterized for a limited length of time by the development of parenchymatous hypertrophy and hyperplasia of the thyroid gland, an increase in heat production, tachycardia, increased reflex irritability and the frequent development of marked exophthalmos, all the reactions so produced closely resembling the syndrome of exophthalmic goiter in man. The administration of an excess of iodine interferes with or prevents the development of the latter as well as the former type of thyroid reaction.

Whether or not cyanide or the extract of the anterior lobe of the pituitary gland is the actual cause of endemic goiter or of exophthalmic goiter, respectively, in man is of minor significance in contrast to the great importance of the fact that there are two types of causes each of which produces very different results, thus indicating the existence of two mechanisms by which the thyroid gland can be affected. The evidence is against the assumption that cyanide is the actual goitrogenic factor which produces endemic goiter in man. Likewise, as yet there is no sound evidence that the thyroid-stimulating factor which produces exophthalmic goiter in man comes from his own pituitary gland.

Iodine deficiency, by which is meant an inadequate supply of iodine for the individual's requirements, causes endemic goiter in man. While the intake of iodine may be sufficient for one person it may not be for others under different or even under apparently similar conditions; various factors influence the individual requirements for iodine, among which are the bacterial flora of the gastro-intestinal tract resulting from filth, from overcrowding of living quarters or similar circumstances, together with a diet containing either inadequate quantities of certain essentials or possibly an excess of other elements. On the other hand, an excess of iodine prevents the development of endemic goiter with its resulting sequelae of cretinism and associated phenomena.

Certain forms of endemic goiter which have developed slowly throughout life in response to a relatively slight or potential hyperthyroidism as a result of iodine deficiency may later in life produce an excess of thyroxine, producing hyperthyroidism; this excess production of thyroxine above, and uncontrolled by, the needs of the individual requirements may in some goitrous persons apparently be precipitated by the administration of an excess of iodine.

The syndrome of exophthalmic goiter is produced by some unknown stimulus acting on the thyroid gland, possibly resembling, but not necessarily identical with, an extract which can be obtained from the anterior lobe of the pituitary gland of cattle. This syndrome is aggravated by a relative deficiency of iodine and is ameliorated by an excess of iodine. Partial thyroidectomy together with the proper administration of iodine cures the disease in a large proportion of patients with minimum mortality.

Exophthalmos and probably some of the other characteristic symptoms of exophthalmic goiter may be secondary to a peculiar irritation or stimulation of the vagosympathetic system. The fact that exophthalmos can be produced in thyroidless animals of certain species but not in others suggests that under the conditions of the experiment a sympathicostimulating substance which will produce exophthalmos can arise from sources other than the thyroid. In man, however, the sympathicostimulating substance probably arises as the result of the as yet unknown cause of the disease acting on the thyroid gland causing it to produce and discharge into the circulation (1) an excess of thyroxine and (2) under conditions of iodine deficiency some intermediate by-product having a peculiar stimulating effect on the vagosympathetic system, possibly tyramine or some similar substance. That the origin of this sympathicostimulating substance is in the thyroid is indicated in man by the fact that partial thyroidectomy, even without the administration of iodine, either abolishes or decreases in the large majority of instances the intensity of the characteristic symptoms of exophthalmic goiter attributable to this substance.

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Book Reviews

The Patient and the Weather. By William F. Petersen. **Volume II. Autonomic Disintegration.** Price, $6.50. Pp. 530, with 249 figures and charts. Ann Arbor, Mich.: Edwards Brothers, Inc., 1934.

This is the second of a coherent series of five or six monographs on the effect of meteorologic factors on the functioning of organs and the localization of disease. Petersen is professor of pathology and bacteriology of the University of Illinois College of Medicine, Chicago. His present thesis is that cyclonic disturbances, which are especially characteristic of the northern tier of states of the United States, bring about stimulation, overstimulation and fatigue of organs and organ systems and in this manner predispose to the localization of disease. While the meteorologic factor is recognized as being only one of several environmental factors in the "constellation of events" which influence the human mechanism, it probably is the most important. In volume I it was shown that the normal person reacts to his meteorologic environment in a chemical and endocrine rhythm conditioned by the recurrent changes of the environment. In volume II are observations on persons who respond excessively to meteorologic change, "in whom clinical reflections become apparent because the chemical and endocrine tides that are set up are unusual in amplitude or because tissue foci exist which cannot adequately accommodate to even the normal swings of the metabolic rhythm." The volume begins with the discussion of vascular spasm and resultant anoxemia, thus setting the stage for the subsequent presentation of the records of cases in a group of pathologic conditions characterized by special susceptibility to changes in the weather. Thus, in migraine, attacks are shown to occur principally in correlation with "cyclonic interfaces," namely, the period of change from the warm, light, more opaque, moist and more heavily ionized air from the south to the cold, clear, dry and less ionized air of the "polar inflow" which follows the passage of the center of the cyclonic disturbance over the given meridian of latitude; the same is true for attacks of epilepsy, eclampsia, mucous colitis, urticaria, asthma, glaucoma and other syndromes. In cases of peptic ulcer the author shows that gastric episodes (hemorrhage and perforation) occur most often in connection with cyclonic interfaces and are probably predicated on pressor changes, also that the distribution of ulcer according to the draft statistics and the mortality statistics of the United States and Canada, is related to the region of the storm tracks. The process of ulcer formation and subsequent periodic aggravation is pictured as follows: "In the meteorologically induced anoxemic stimulation . . . the mucosa of the stomach participates in a degree that will be greater in the unstable and poorly buffered individual. . . . Hyperacidity is the manifestation of the stimulation of the mucosa and the implication of the great need for proper oxygenation," but spasm follows and more anoxemia results from this. Thus dyskinesia exists. A great demand for oxygen is created in a mucous membrane, with spasm of its nutrient arteries and consequent anoxemia; stimulation of the tissues is augmented by the anoxemia to the stage of fatigue, and death of the tissue follows. This dysfunction of the vascular supply in ulcer has been recognized by other investigators. The feature that Petersen adds is the recognition of the meteorologic basis of the underlying autonomic dysfunction.

The clinical investigation of many cases presented under the different headings is large, involving elaborate data on blood chemistry, with analyses repeated usually every day for long periods. There are also many detailed records of clinical observations. This evidence seems to sustain the author's contentions, but the burden of proof rests with him, and one gets the impression throughout that much is suggested and little actually proved. Thus, periods of meteorologic disturbance

with no corresponding deviations in the blood pressure and blood chemistry factors and no symptoms occur with disturbing frequency in all the illustrative cases, and clinical episodes, the attacks of epilepsy, for instance, appear sometimes in other stages of the cyclonic periods and by no means regularly at the interfaces of the tropical and polar airs. At least so it seems from examination of the complicated graphs. The data are presented for the most part in these graphs, and unfortunately they are constructed so confusedly as to be almost illegible.

Petersen takes strenuous objection to the tendency in medicine to study detail and to neglect the patient as a whole. However, the avoiding of this error, in emulation of Hippocrates, carries with it the danger of becoming satisfied with generalities and less concerned about actual proofs.

A major difficulty in the study of environment is the enormous complexity involved. Physical, chemical and psychic factors are so multiple that their proper evaluation may not be possible with the means at hand today. The effects of the weather, contrary to Petersen's opinion, are not ignored by wise physicians, even by those who consider that their chief responsibility is to arrive at "a definite diagnosis, particularly in acute conditions." It is widely recognized that more exact knowledge of the effect of weather on disease is badly needed, and it can be safely affirmed that the effort of Petersen and his associates to define the importance of meteorology in medicine will be highly commended, whether or not the conclusions will withstand the criticisms that they will provoke.

De Venarum Ostiolis 1603 of Hieronymus Fabricius ab Aquapendente (1533?-1619). Facsimile edition with introduction, translation and notes by K. J. Franklin, D.M., Tutor and Lecturer in Physiology of Oriel College and University Demonstrator of Pharmacology, Oxford. Price, $3 postpaid. Pp. 104, with 7 figures and 8 plates. Springfield, Ill.: Charles C. Thomas, Publisher, 1933.

The pamphlet on the valves of the heart of twenty-three pages was described as but one of the "remaining pamphlets, and of that large work, which we are compiling on the structure of the animal as a whole" (Fabricius). It is thus but a chapter of a contemplated work on the anatomy of the body which was never completed. Fabricius observed that he noted the valves first in 1574 and demonstrated them to his students, including William Harvey, before he published his account of them in 1603—the year after Harvey left Padua. According to Boyle, Harvey, in a private conversation, confided to him "that when he took notice of the Valves in the Veins of so many several Parts of the Body Towards the Heart, but opposed the passage of the Venal Blood the Contrary way: He was invited to imagine . . . That, since the Blood could not well, because of the interposing Valves, be Sent by the Veins to the Limbs; it should be Sent through the Arteries, and Return through the Veins, whose Valves did not oppose its course that way." Fabricius was not the first to either describe the valves or picture them. He was, however, the first to demonstrate them publicly and describe them in detail. Besides the facsimile with its seven plates and translation, this book contains an account of the life of Fabricius, the early history of work on the venous valves, a description of the anatomic theater of the school of anatomy at Padua and a detailed account of the size of the original pages and plates, besides references. In every respect this book is a worthy Thomas publication and one of paramount interest to medical historians.

Sex Hygiene: What to Teach and How to Teach It. By Alfred Worcester, M.D., Henry K. Oliver Professor of Hygiene, Harvard University. Price, $2.50. Pp. 136. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

Ten years ago in Boston a dinner was given in honor of Dr. Alfred Worcester because his seventieth birthday was approaching. It was said at the time that he represented as well as any one could a physician who had been a strenuous youth

for seventy years and who always had been a pioneer and a crusader—a pioneer in introducing new methods for being more helpful to humanity and a crusader in attacking fearlessly all abuses within the medical profession. It is not surprising, therefore, that at 79, still young at heart, still a pioneer and still a crusader, he should assemble a book defining his conception of that much abused term "sex hygiene" and describing how, as professor of hygiene at Harvard University, he has found this subject can best be taught.

The volume is a collection of essays illustrating how Dr. Worcester more than thirty years ago first came to feel the need for teaching sex hygiene in schools and colleges and how, step by step, he evolved a method for doing this satisfactorily. Certain persons may not agree with all his views or may believe that much of what he accomplishes depends on his own personality rather than on his methods of teaching. This, however, does not detract from the value of his book, which is a personal work, pretending to do no more than state the author's own ideas on the topics which he discusses. These essays have been collected for the assistance of teachers primarily. Physicians, parents and students will also find the volume worth reading, for it deals with matters pertaining to sex logically and with all the sincerity, honesty and fine idealism of the author.

Rheumaprobleme. Band III. Gesammelte Vorträge gehalten auf dem III. Ärztekursus des Rheuma-Forschungs-Instituts am Landesbad der Rheinprovinz in Aachen. Paper. Price, 5.40 marks. Pp. 95. Leipzig: Georg Thieme, 1934.

Extensive researches on rheumatic diseases are being fostered in various countries through the efforts of national groups and committees. Those carried on in Germany are among the most important. The collected reports of the Third Congress held at the Rheuma-Forschungs-Institut in Aachen are published in this volume, which contains eleven contributions by the following: Aschoff (Freiburg in Breisgau), Edens and Manteufel (Düsseldorf), Grashey and Külbs (Köln), Kreuz (Berlin), Schottmüller (Hamburg) and Krebs, Gehlen, Hennes and Vontz (Aachen). Various phases of rheumatic diseases are discussed, including researches on the etiology of rheumatic myocarditis and the significance of bodily constitution in the production of rheumatic diseases. There are several papers on the therapy of the "specific rheumatic infections," arthritis, arthrosis, rheumatic diseases of the vertebral column, myalgia and neuralgia by various means: medicinal treatment, roentgen rays and other physical means.

Previous conferences were held in 1928 and 1930, and reports of their agenda appeared in 1929 and 1931.

Revista argentina de cardiologia. A bimonthly journal. Volume I, no. 2. Paper. Price, $6 per year. Pp. 180. With illustrations and charts. Published under the supervision of the editorial board, Buenos Aires, 1934.

This is the second issue of this journal that was introduced during the current year. This number contains three original articles. The first deals with the optical recording of heart sounds; the second discusses gallop rhythm from the same standpoint, and the third shows the effect that may be produced on the electrocardiogram by suspending the heart in saline solution.

A case is reported, with a discussion of a shifting cardiac rhythm in connection with Cheyne-Stokes' respiration. This is followed by a short discussion of the causes of cyanosis in Ayerza's disease. The remainder of the book is devoted to abstracts of articles from the current literature.

The journal is well printed on an excellent quality of paper, and the illustrations are remarkably clear. It is probable that Spanish is less widely read than it should be. Apparently realizing this fact, the editors have added to each of the articles a summary in French, German and English. This journal should be warmly welcomed into literature on cardiovascular disease.

A Textbook of Biochemistry. Edited by Benjamin Harrow, Ph.D., Associate Professor of Chemistry, the City College, College of the City of New York, and Carl P. Sherwin, M.D., Sc.D., Dr.P.H., LL.D., member of the staff of St. Vincent's Hospital and French Hospital, New York City. Cloth. Price, $6. Pp. 797, with 52 illustrations. Philadelphia: W. B. Saunders Company, 1935.

Composite textbooks of medicine have become common in this country, but so far as the reviewer knows this is the first textbook of biochemistry to be compiled in this way. The obvious advantage of having experts deal with their special fields seems fulfilled when one finds among the authors of various sections such men as McCollum, Bloor, Drummond, Heidelberger, Luck and many others of equal prestige. The subject matter (too extensive to attempt to review in detail) is, for the most part, well presented, each section being followed by a bibliography of outstanding articles or reviews. While one misses the coherent point of view of a one-man book, one doubts whether any one person could cover the subject so adequately.

Treatment by Diet. By Clifford J. Barborka. Price, $5. Pp. 615, with 8 illustrations. Philadelphia: J. B. Lippincott Company, 1934.

In this excellent compendium Dr. Barborka seems to have reduced to its simplest terms the subject of treatment by diet. The preliminary matters of diet in health, methods of calculating diets and serving meals and other phases of the subject are presented concisely in forty-two pages. Diseases are divided into those in which diet is of paramount importance, such as diabetes, and those in which it is of varying importance. In each instance, however, there is a brief preliminary statement of the nature of the disease in question and the particular dietetic objectives. This is followed by simple general discussions, and then by many detailed lists of diets.

While the reviewer disagrees with Barborka on small points here and there, all will agree that the general principles brought out are sound. On the whole, this is the most useful "practical" book on diet that the reviewer knows of.

The Heart Visible. By J. Polevski. Price, $5. Pp. 207, with 122 illustrations. Philadelphia: F. A. Davis Company, 1934.

Disguised behind this preposterous title one finds an excellent discussion of cardiovascular roentgenology. Most of the material is accessible in scattered textbooks on cardiology and roentgenology but, as Polevski points out, there is no short book in English in which the subject is taken up in monographic form. An outstanding feature is the large number of good reproductions of roentgenograms around which the text is built; the exposition is clear and the style pleasant. Perhaps Polevski goes a bit far when he states (preface, p. 4) that "a careful fluoroscopic examination is almost equivalent to dissection in vivo," but, on the other hand, it is only fair to say that most physicians do not fully appreciate the detailed information which can be gleaned from careful roentgen study of the heart and aorta. There are a good bibliography and an index.

Diabetic Manual for Patients. By Henry J. John. Second edition. Price, $1.50. Pp. 232, with 47 illustrations. St. Louis: C. V. Mosby Company, 1934.

The first edition of this manual appeared in 1928. The ARCHIVES OF INTERNAL MEDICINE (**42**:610 [Oct.] 1928) and the *Journal of the American Medical Association* (**91**:1928 [Oct. 20] 1928) contained reviews of it, both reviews speaking well of the book. The second edition is a few pages longer than the first and has a few more illustrations. The manual continues to be an intelligent booklet, useful for both diabetic patients and practitioners or students who wish to brush up on practical diabetic therapy. Once again it is pleasant to notice that the author refers to diabetic manuals already in existence as reading matter recommendable to patients.